Complete Summary

GUIDELINE TITLE

2001 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus.

BIBLIOGRAPHIC SOURCE(S)

2001 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus. Rockville (MD): U.S. Department of Health and Human Services, Public Health Service; 2001 Nov 28. 64 p. [145 references]

Centers for Disease Control and Prevention. Guidelines for preventing opportunistic infections among HIV-infected persons -- 2002. Recommendations of the U.S. Public Health Service and the Infectious Diseases Society of America. MMWR Recomm Rep 2002 Jun 14;51(RR-8):1-52. [145 references]

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

- Human immunodeficiency virus (HIV)
- Acquired immunodeficiency syndrome (AIDS)
- Pneumocystis carinii pneumonia
- Toxoplasmic encephalitis
- Cryptosporidiosis
- Microsporidiosis
- Tuberculosis
- Disseminated infection with Mycobacterium avium complex
- Bacterial respiratory infections
- Bacterial enteric infections
- Bartonellosis
- Candidiasis
- Cryptococcosis

- Histoplasmosis
- Coccidioidomycosis
- Cytomegalovirus disease
- Herpes simplex virus disease
- Varicella-zoster virus infection
- Human herpesvirus 8 infection (Kaposi's Sarcoma-Associated Herpes Virus)
- Human papillomavirus infection
- Hepatitis C virus infection

GUIDELINE CATEGORY

Prevention

CLINICAL SPECIALTY

Family Practice
Infectious Diseases
Internal Medicine
Obstetrics and Gynecology
Pediatrics
Preventive Medicine

INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel
Health Care Providers
Nurses
Patients
Physician Assistants
Physicians
Public Health Departments

GUIDELINE OBJECTIVE(S)

- To present disease-specific recommendations for the prevention of opportunistic infections in HIV-infected persons by preventing exposure to the opportunistic pathogen, preventing the first episode of disease, and preventing disease recurrence
- To update the 1999 recommendations

TARGET POPULATION

Human immunodeficiency virus (HIV) infected persons in the United States and other industrialized countries.

INTERVENTIONS AND PRACTICES CONSIDERED

Prevention

1. Patient education and counseling regarding sources of infection and ways to avoid exposure to opportunistic pathogens:
    - Sexual exposure prevention (condom use, dental dams, latex gloves, and avoiding sexual practices that might result in oral exposure to feces)
    - Avoiding injection drug use exposures
    - Reducing environmental and occupational exposures
    - Avoiding pet-related exposures (risk with cats, birds, reptiles)
    - Avoiding food and water-related exposures
    - Avoiding travel-related exposures
2. Appropriate preventive testing, including:
    - Testing for immunoglobulin G (IgG) antibody to Toxoplasma
    - Tuberculin skin test by administration of intermediate-strength (5-TU) purified protein derivative (PPD) by the Mantoux method
    - Chest radiography and clinical evaluation as appropriate
    - Testing for antibody to cytomegalovirus
    - Pelvic examination and Pap smear to evaluate for papillomavirus-associated genital epithelial cancers in HIV-infected women followed by treatment of any abnormalities
    - Screening for hepatitis B markers
    - Screening hepatitis C virus infection by using enzyme immunoassays (EIAs) licensed for detection of antibody to hepatitis C virus
3. Disease-specific prophylaxis to prevent the first episode of disease, and/or disease recurrence, including:
    - Acyclovir
    - Amantadine
    - Amphotericin B
    - Ampicillin
    - Aerosolized pentamidine
    - Atovaquone
    - Azithromycin
    - Cefotaxime
    - Ceftriaxone
    - Chloramphenicol
    - Cidofovir
    - Ciprofloxacin
    - Clarithromycin
    - Clindamycin
    - Dapsone
    - Doxycycline
    - Erythromycin
    - Ethambutol
    - Famciclovir
    - Fluconazole
    - Fluoroquinolones
    - Fomivirsen
    - Foscarnet
    - Ganciclovir
    - Granulocyte-colony-stimulating factor (G-CSF)
    - Granulocyte-macrophage colony-stimulating factor (GM-CSF)
    - Hepatitis A vaccine
    - Hepatitis B vaccine
    - Inactivated influenza virus (influenza A or B)

- Intravenous immunoglobulin
- Isoniazid
- Itraconazole
- Leucovorin
- Oseltamivir
- Pyrazinamide
- Pyridoxine
- Pyrimethamine
- Respiratory syncytial virus (RSV) antibody
- Rifabutin
- Rifampin
- Rimantadine
- Sulfadiazine
- Trimethoprim-sulfamethoxazole (TMP-SMZ)
- Valacyclovir
- Valganciclovir
- Varicella zoster immune globulin

4. Disease-specific practices for the discontinuation of primary and/or secondary prophylaxis
5. Disease-specific prevention practices appropriate for children and pregnant women with HIV
6. Vaccination for patients (23-valent polysaccharide pneumococcal, hepatitis A, hepatitis B, influenza)
7. Routine immunizations for children with HIV

MAJOR OUTCOMES CONSIDERED

- Incidence of opportunistic infection
- Morbidity and mortality
- Feasibility, efficacy, and cost of preventive measures
- Impact of intervention on quality of life
- Toxicities, drug interactions, and the potential to induce drug resistance

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The guideline developers performed a Medline search to support the development of the guidelines. During the development of the revised guidelines, working group members reviewed published manuscripts as well as abstracts and material presented at professional meetings.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Quality of evidence supporting the recommendation:

Category: I
Definition: Evidence from at least one properly randomized, controlled trial.

Category: II
Definition: Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than one center), or from multiple time-series. Or dramatic results from uncontrolled experiments.

Category: III
Definition: Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not applicable

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Strength of the recommendation:

Rating: A
Strength of the recommendation: Both strong evidence for efficacy and substantial clinical benefit support recommendation for use.
Should always be offered.

Rating: B
Strength of the recommendation: Moderate evidence for efficacy -- or strong evidence for efficacy but only limited clinical benefit -- supports recommendation for use.
Should generally be offered.

Rating: C
Strength of the recommendation: Evidence for efficacy is insufficient to support a recommendation for or against use. Or evidence for efficacy might not outweigh adverse consequences (e.g., drug toxicity, drug interactions) or cost of the chemoprophylaxis or alternative approaches. Optional.

Rating: D
Strength of the recommendation: Moderate evidence for lack of efficacy or for adverse outcome supports a recommendation against use. Should generally not be offered.

Rating: E
Strength of the recommendation: Good evidence for lack of efficacy or for adverse outcome supports a recommendation against use. Should never be offered.

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

These guidelines were made available for public comment through announcements published in the Federal Register and the Morbidity and Mortality Weekly Report (MMWR).

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Please note: June 6, 2003 Guidelines for Environmental Infection Control in Health-Care Facilities. Recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee (HICPAC), published by the Centers for Disease Control and Prevention (CDC) provides supplemental information regarding patient interaction with pets and animals in the home.

Levels of evidence (I-III) and grades of recommendation (A-E) ratings are defined at the end of the Major Recommendations field.

MAJOR CHANGES IN THE GUIDELINES SINCE 1999 INCLUDE:

- Higher level ratings have been provided for discontinuing primary prophylaxis for Pneumocystis carinii pneumonia (PCP) and Mycobacterium avium complex (MAC) when CD4+ T lymphocytes have increased to >200 cells/microliter and

>100 cells/microliter, respectively, for ≥3 months in response to highly active antiretroviral therapies (HAART) (rating: AI), and a new recommendation to discontinue primary Toxoplasma prophylaxis has been provided when the CD4+ T lymphocyte count has increased to >200 cells/microliter for ≥3 months (rating: AI).

- Secondary Pneumocystis carinii pneumonia prophylaxis should be discontinued in patients whose CD4+ counts have increased to >200 cells/microliter for ≥3 months as a consequence of highly active antiretroviral therapies (rating: BII).
- Secondary prophylaxis for disseminated Mycobacterium avium complex may be discontinued in patients with a sustained (e.g., ≥6 months) increase in CD4+ count to >100 cells/microliter in response to highly active antiretroviral therapies if they have completed 12 months of Mycobacterium avium complex therapy and have no symptoms or signs attributable to Mycobacterium avium complex (rating: CIII).
- Secondary prophylaxis for toxoplasmosis and cryptococcosis may be discontinued in patients with a sustained increase in CD4+ counts (e.g. ≥6 months) to >200 cells/microliter and >100 to 200 cells/microliter respectively, in response to highly active antiretroviral therapies if they have completed their initial therapy and have no symptoms or signs attributable to these pathogens (rating: CIII).
- The importance of screening all HIV-infected individuals for hepatitis C virus (HCV) is emphasized (rating: BIII).
- Additional information about transmission of human herpesvirus 8 infection (HHV-8) is provided.
- New information on drug interactions is provided, especially with regard to rifamycins and antiretroviral drugs.
- Revised recommendations for immunization of HIV exposed/infected adults and children are provided.

DISEASE-SPECIFIC RECOMMENDATIONS:

Pneumocystis carinii Pneumonia

Prevention of Exposure

1. Although some authorities recommend that persons with human immunodeficiency virus (HIV) infection who are at risk for Pneumocystis carinii pneumonia (PCP) not share a hospital room with a patient who has Pneumocystis carinii pneumonia, data are insufficient to support this recommendation as standard practice (rating: CIII).

Prevention of Disease

Initiation of Primary Prophylaxis

2. Adults and adolescents who have HIV infection (including pregnant women and those on highly active antiretroviral therapies) should receive chemoprophylaxis against Pneumocystis carinii pneumonia if they have a CD4+ T-lymphocyte count of less than 200/microliter (rating: AI) or a history of oropharyngeal candidiasis (rating: AII) (Phair et al, 1990; Kaplan et al, 1998; CDC, 1989). Persons who have a CD4+ T-lymphocyte percentage of

less than 14% or history of an acquired immunodeficiency syndrome (AIDS)-defining illness but do not otherwise qualify should be considered for prophylaxis (rating: BII) (Phair et al, 1990; Kaplan et al, 1998; CDC, 1989). When monitoring the CD4+ T-lymphocyte count at least every 3 months is not possible, initiation of chemoprophylaxis at a CD4+ T-lymphocyte count of greater than 200 but less than 250 cells/microliter also should be considered (rating: BII) (Kaplan et al, 1998).

3. Trimethoprim-sulfamethoxazole (TMP-SMZ) is the recommended prophylactic agent (rating: AI) (CDC, 1989; Bozzette et al, 1995; Schneider et al, 1992; Schneider et al, 1995). One double-strength tablet per day is the preferred regimen (rating: AI) (Schneider et al, 1995). However, one single-strength tablet per day (Schneider et al, 1995) is also effective and might be better tolerated (rating: AI). One double-strength tablet three times per week is also effective (rating: BI) (El-Sadr et al, 1999). Trimethoprim-sulfamethoxazole at a dose of one double-strength tablet per day confers cross-protection against toxoplasmosis (Carr, et al. (1992) and some common respiratory bacterial infections (Bozzette et al, 1995; Hardy et al, 1992). Lower doses of trimethoprim-sulfamethoxazole also might confer such protection. For patients who have an adverse reaction that is not life-threatening, treatment with trimethoprim-sulfamethoxazole should be continued if clinically feasible; for those who have discontinued such therapy because of an adverse reaction, reinstitution of trimethoprim-sulfamethoxazole should be strongly considered after the adverse event has resolved (rating: AII). Patients who have experienced adverse events, especially fever and rash, might better tolerate reintroduction of the drug with a gradual increase in dose (desensitization) as per published regimens (rating: BI) (Leoung et al, 1997; Para et al, 2000) or reintroduction of trimethoprim-sulfamethoxazole at a reduced dose or frequency (rating: CIII); up to 70% of patients can tolerate such reinstitution of therapy Para et al, 2000).
4. If trimethoprim-sulfamethoxazole cannot be tolerated, prophylactic regimens that can be recommended as alternatives include dapsone (rating: BI), (Bozzette et al, 1995) dapsone plus pyrimethamine plus leucovorin (rating: BI) (Podzamczer et al, 1995; Opravil et al, 1995), aerosolized pentamidine administered by the Respirgard II™ nebulizer (Marquest, Englewood, Colorado) (rating: BI), (Schneider et al, 1992) and atovaquone (rating: BI) (Chan et al, 1999; El-Sadr et al, 1998. Atovaquone appears to be as effective as aerosolized pentamidine (Chan et al, 1999) or dapsone (rating: BI) (El-Sadr et al, 1998) but is substantially more expensive than the other regimens. For patients seropositive for Toxoplasma gondii who cannot tolerate trimethoprim-sulfamethoxazole, recommended alternatives to trimethoprim-sulfamethoxazole for prophylaxis against both Pneumocystis carinii pneumonia and toxoplasmosis include dapsone plus pyrimethamine (rating: BI) (Podzamczer et al,1995; Opravil et al, 1995) or atovaquone with or without pyrimethamine (rating: CIII). The following regimens generally cannot be recommended as alternatives because data regarding their efficacy for Pneumocystis carinii pneumonia prophylaxis are insufficient for a firm recommendation: aerosolized pentamidine administered by other nebulization devices, intermittently administered parenteral pentamidine, oral pyrimethamine plus sulfadoxine, oral clindamycin plus primaquine, and intravenous trimetrexate. However, clinicians may consider using these agents in unusual situations in which the recommended agents cannot be administered (rating: CIII).

Discontinuation of Primary Prophylaxis

5. Primary pneumocystis prophylaxis should be discontinued in adult and adolescent patients who have responded to highly active antiretroviral therapies with an increase in CD4+ T lymphocyte counts to >200 cells/microliter for at least 3 months (rating: AI). In observational and randomized studies supporting this recommendation, most patients were taking antiretroviral regimens that included a protease inhibitor and most had a CD4+ cell counter greater than 200 cells/microliter for at least 3 months before discontinuation of Pneumocystis carinii pneumonia prophylaxis (Furrer, Egger, Opravil, et al, 1999; Weverling, et al, 1999; Yangco et al, 2000; Schneider, Borleffs, Stolk, et al,. 1999; Furrer, Opravil, Rossi et al, 2001). The median CD4+ lymphocyte count at the time prophylaxis was discontinued was >300 cells/microliter, and many patients had a sustained suppression of HIV plasma ribonucleic acid levels below detection limits of the assay employed. Median follow-up ranged from 6 to 16 months.

Discontinuation of primary prophylaxis in these patients is recommended not only because prophylaxis appears to add very little to disease prevention (for Pneumocystis carinii pneumonia, toxoplasmosis, or bacterial infections), but also because discontinuation of drug reduces pill burden, the potential for drug toxicity, drug interactions, selection of drug-resistant pathogens, and cost.

Restarting Primary Prophylaxis

6. Prophylaxis should be reintroduced if the CD4+ T lymphocyte count decreases to <200 cells/microliter (rating: AIII).

Prevention of Recurrence

7. Patients who have a history of Pneumocystis carinii pneumonia should be administered chemoprophylaxis (i.e., secondary prophylaxis or chronic maintenance therapy) with the regimens listed in Table 2 of the original guideline document for life (rating: AI) unless immune reconstitution occurs as a consequence of highly active antiretroviral therapies (see Recommendation No. 8, below).

Discontinuation of Secondary Prophylaxis (Chronic Maintenance Therapy)

8. Secondary prophylaxis should be discontinued for adult and adolescent patients whose CD4+ T cell count has increased from <200 cells/microliter to >200 cells/microliter for at least 3 months due to highly active antiretroviral therapies (rating: BII). Reports from observational studies (Dworkin et al, 2000; Kirk et al, 1999; Soriano et al., 2000) and from a randomized trial, (Lopez Bernaldo de Quiros, 2001) as well as a combined analysis of 8 European cohorts being followed prospectively, (Ledergerber et al, 2001) support this recommendation. In these studies, patients had responded to highly active antiretroviral therapies with an increase in CD4+ T-lymphocyte count to >200 cells/microliter for at least 3 months. Most patients were taking protease inhibitor-containing regimens. The median CD4+ T-lymphocyte count at the time prophylaxis was discontinued was >300 cells/microliter. Most patients had sustained suppression of HIV plasma HIV

ribonucleic acid levels below the detection limits of the assay employed; the longest follow-up was 13 months. If the episode of Pneumocystis carinii pneumonia occurred at a CD4+ T lymphocyte count >200 cells/microliter, it is probably prudent to continue Pneumocystis carinii pneumonia prophylaxis for life regardless of how high the CD4+ T lymphocyte count rises as a consequence of highly active antiretroviral therapies (rating: CIII).

Discontinuation of secondary prophylaxis for patients is recommended not only because prophylaxis appears to add very little to disease prevention (for Pneumocystis carinii pneumonia, toxoplasmosis, or bacterial infections), but also because discontinuation of drug reduces pill burden, the potential for drug toxicity, drug interactions, and selection of drug resistant pathogens, and cost.

Restarting Secondary Prophylaxis

9. Prophylaxis should be reintroduced if the CD4+ T lymphocyte count decreases to <200 cells/microliter (rating: AIII), or if Pneumocystis carinii pneumonia recurred at a CD4+ T lymphocyte count >200 cells/microliter (rating: CIII).

Special Considerations

Children

10. Children born to HIV-infected mothers should be administered prophylaxis with trimethoprim-sulfamethoxazole beginning at 4 to 6 weeks of age (CDC, 1995) (rating: AII). Prophylaxis should be discontinued for children who are subsequently found not to be infected with HIV. HIV-infected children and children whose infection status remains unknown should continue to receive prophylaxis for the first year of life. The need for subsequent prophylaxis should be determined on the basis of age-specific CD4+ T-lymphocyte count thresholds (see Table 11 in the original guideline document) (rating: AII). The safety of discontinuing prophylaxis in HIV-infected children receiving highly active antiretroviral therapies has not been studied extensively.
11. Children who have a history of Pneumocystis carinii pneumonia should be administered lifelong chemoprophylaxis to prevent recurrence (CDC, 1995) (rating: AI). The safety of discontinuing secondary prophylaxis in HIV-infected children has not been studied extensively.

Pregnant Women

12. Chemoprophylaxis for Pneumocystis carinii pneumonia should be administered to pregnant women as is done for other adults and adolescents (rating: AIII). Trimethoprim-sulfamethoxazole is the recommended prophylactic agent; dapsone is an alternative. Because of theoretical concerns regarding possible teratogenicity associated with drug exposures during the first trimester, providers may choose to withhold prophylaxis during the first trimester. In such cases, aerosolized pentamidine may be considered because of its lack of systemic absorption and the resultant lack of exposure of the developing embryo to the drug (rating: CIII).

Toxoplasmic Encephalitis

Prevention of Exposure

1. HIV-infected persons should be tested for immunoglobulin G (IgG) antibody to Toxoplasma soon after the diagnosis of HIV infection to detect latent infection with Toxoplasma gondii (rating: BIII).
2. All HIV-infected persons, but particularly those who lack immunoglobulin G antibody to Toxoplasma, should be counseled about the various sources of toxoplasmic infection. They should be advised not to eat raw or undercooked meat, particularly undercooked beef, pork, lamb, or venison (rating: BIII). Specifically, lamb, beef, and pork should be cooked to an internal temperature of 165 to 170 degrees F; meat cooked until it is no longer pink inside generally has an internal temperature of 165 to 170 degrees F (CDC, 1995) and therefore satisfies this requirement. HIV-infected persons should wash their hands after contact with raw meat and after gardening or other contact with soil; in addition, they should wash fruits and vegetables well before eating them raw (rating: BIII). If the patient owns a cat, the litter box should be changed daily, preferably by an HIV-negative, nonpregnant person; alternatively, the patient should wash the hands thoroughly after changing the litter box (rating: BIII). Patients should be encouraged to keep their cats inside and not to adopt or handle stray cats (rating: BIII). Cats should be fed only canned or dried commercial food or well-cooked table food, not raw or undercooked meats (rating: BIII). Patients need not be advised to part with their cats or to have their cats tested for toxoplasmosis (rating: EII).

Prevention of Disease

Initiation of Primary Prophylaxis

3. Toxoplasma-seropositive patients who have a CD4+ T-lymphocyte count of less than 100/microliter should be administered prophylaxis against toxoplasmic encephalitis (TE) (rating: AII) (Carr et al, 1992). The double-strength tablet daily dose of trimethoprim-sulfamethoxazole recommended as the preferred regimen for Pneumocystis carinii pneumonia prophylaxis appears to be effective against toxoplasmic encephalitis as well and is therefore recommended (rating: AII) (Carr et al, 1992). If patients cannot tolerate trimethoprim-sulfamethoxazole, the recommended alternative is dapsone-pyrimethamine, which is also effective against Pneumocystis carinii pneumonia (rating: BI) (Podzamczer et al, 1995; Opravil et al, 1995). Atovaquone with or without pyrimethamine also may be considered (rating: CIII). Prophylactic monotherapy with dapsone, pyrimethamine, azithromycin, or clarithromycin cannot be recommended on the basis of current data (rating: DII). Aerosolized pentamidine does not protect against toxoplasmic encephalitis and is not recommended (rating: EI) (Bozette et al., 1995; Carr et al., 1992)
4. Toxoplasma-seronegative persons who are not taking a Pneumocystis carinii pneumonia prophylactic regimen known to be active against toxoplasmic encephalitis should be retested for immunoglobulin G antibody to Toxoplasma when their CD4+ T-lymphocyte count declines below 100/microliter to determine whether they have seroconverted and are therefore at risk for toxoplasmic encephalitis (rating: CIII). Patients who have seroconverted should be administered prophylaxis for toxoplasmic encephalitis as described above (rating: AII).

Discontinuation of Primary Prophylaxis

5. Prophylaxis against toxoplasmic encephalitis should be discontinued in adult and adolescent patients who have responded to highly active antiretroviral therapies with an increase in CD4+ T-lymphocyte counts to >200 cells/microliter for at least 3 months (rating: AI). Several observational studies (Dworkin et al, 2000; Kirk et al, 1999; Furrer et al, 2000) and two randomized trials (Mussini et al, 2000; Miro et al, 2000) have shown that primary prophylaxis can be discontinued with minimal risk of developing toxoplasmic encephalitis in patients who have responded to highly active antiretroviral therapies with an increase in CD4+ T lymphocyte count from <200 cells/microliter to >200 cells/microliter for at least 3 months. In these studies, most patients were taking protease inhibitor-containing regimens and the median CD4+ T-lymphocyte count at the time prophylaxis was discontinued was >300 cells/microliter. At the time prophylaxis was discontinued, many patients had sustained suppression of plasma HIV ribonucleic acid levels below the detection limits of available assays; the median follow up ranged from 7 to 22 months

While patients with CD4+ T lymphocyte counts of <100 cells/microliter are at greatest risk for developing toxoplasmic encephalitis, the risk of toxoplasmic encephalitis occurring when the CD4+ T-lymphocyte count has increased to 100 to 200 cells/microliter has not been studied as rigorously as a rise to >200 cells/microliter. Thus, the recommendation specifies discontinuation of prophylaxis after an increase to >200 cells/microliter.

Discontinuation of primary toxoplasmic encephalitis prophylaxis is recommended not only because prophylaxis appears to add very little to disease prevention for toxoplasmosis, but also because discontinuation of drug reduces pill burden, the potential for drug toxicity, drug interaction, and selection of drug resistant pathogens.

Restarting Primary Prophylaxis

6. Prophylaxis should be reintroduced if the CD4+ T lymphocyte count decreases to <100-200 cells/microliter (rating: AIII).

Prevention of Recurrence

7. Patients who have completed initial therapy for toxoplasmic encephalitis should be administered lifelong suppressive therapy (secondary prophylaxis or chronic maintenance therapy) (rating: AI) (Katlama et al, 1996; Dannemann et al, 1992) unless immune reconstitution occurs as a consequence of highly active antiretroviral therapies (see Recommendation No. 8, below). The combination of pyrimethamine plus sulfadiazine plus leucovorin is highly effective for this purpose (rating: AI). A commonly used regimen for patients who cannot tolerate sulfa drugs is pyrimethamine plus clindamycin (rating: BI); however, only the combination of pyrimethamine plus sulfadiazine appears to provide protection against Pneumocystis carinii pneumonia as well (rating: AII).

Discontinuation of Secondary Prophylaxis (Chronic Maintenance Therapy)

8. Adult and adolescent patients receiving secondary prophylaxis (chronic maintenance therapy) for toxoplasmic encephalitis appear to be at low risk for recurrence of toxoplasmic encephalitis when they have successfully completed initial therapy for toxoplasmic encephalitis, remain asymptomatic with respect to signs and symptoms of toxoplasmic encephalitis, and have a sustained increase in their CD4+ T-lymphocyte counts to >200 cells/microliter following highly active antiretroviral therapies (e.g., ≥6 months) (Kirk et al, 1999; Soriano et al, 2000; Miro et al, 2000). While the numbers of patients who have been evaluated remain small and occasional recurrences have been seen, based on these observations and on inference from more extensive cumulative data suggesting the safety of discontinuation of secondary prophylaxis for other opportunistic infections during advanced HIV disease, it is reasonable to consider discontinuation of chronic maintenance therapy in such patients (rating: CIII). Some experts would obtain a magnetic resonance image of the brain as part of their evaluation to determine whether or not discontinuation of therapy is appropriate.

Restarting Secondary Prophylaxis

9. Secondary prophylaxis (chronic maintenance therapy) should be reintroduced if the CD4+ T lymphocyte count decreases to <200 cells/microliter (rating: AIII).

Special Considerations

Children

10. Trimethoprim-sulfamethoxazole, when administered for Pneumocystis carinii pneumonia prophylaxis, also provides prophylaxis against toxoplasmosis. Atovaquone might also provide protection (rating: CIII). Children aged greater than 12 months who qualify for Pneumocystis carinii pneumonia prophylaxis and who are receiving an agent other than trimethoprim-sulfamethoxazole or atovaquone should have serologic testing for Toxoplasma antibody (rating: BIII), because alternative drugs for Pneumocystis carinii pneumonia prophylaxis might not be effective against Toxoplasma. Severely immunosuppressed children who are not receiving trimethoprim-sulfamethoxazole or atovaquone who are found to be seropositive for Toxoplasma should be administered prophylaxis for both Pneumocystis carinii pneumonia and toxoplasmosis (i.e., dapsone plus pyrimethamine) (rating: BIII). Children with a history of toxoplasmosis should be administered lifelong prophylaxis to prevent recurrence (rating: AI). The safety of discontinuing primary or secondary prophylaxis in HIV-infected children receiving highly active antiretroviral therapies has not been studied extensively.

Pregnant Women

11. Trimethoprim-sulfamethoxazole can be administered for prophylaxis against toxoplasmic encephalitis as described for Pneumocystis carinii pneumonia (rating: AIII). However, because of the low incidence of toxoplasmic encephalitis during pregnancy and the possible risk associated with pyrimethamine treatment, chemoprophylaxis with pyrimethamine-containing

regimens can reasonably be deferred until after pregnancy (rating: CIII). For prophylaxis against recurrent toxoplasmic encephalitis, the healthcare provider and clinician should be well informed about the benefit of lifelong therapy and the concerns about teratogenicity of pyrimethamine. Guidelines outlined in Nos. 7 through 9, above, should be used when making decisions regarding secondary prophylaxis for toxoplasmic encephalitis in pregnancy.

12. In rare cases, HIV-infected pregnant women who have serologic evidence of remote toxoplasmic infection have transmitted Toxoplasma to the fetus in utero. Pregnant HIV-infected women who have evidence of primary toxoplasmic infection or active toxoplasmosis (including toxoplasmic encephalitis) should be evaluated and managed during pregnancy in consultation with appropriate specialists (rating: BIII). Infants born to women who have serologic evidence of infections with HIV and Toxoplasma should be evaluated for congenital toxoplasmosis (rating: BIII).

Cryptosporidiosis

Prevention of Exposure

1. HIV-infected persons should be educated and counseled about the many ways that Cryptosporidium can be transmitted (rating: BIII). Modes of transmission include having direct contact with infected adults, diaper-aged children, and infected animals; drinking contaminated water; coming into contact with contaminated water during recreational activities; and eating contaminated food.
2. HIV-infected persons should avoid contact with human and animal feces. They should be advised to wash their hands after contact with human feces (e.g., diaper changing), after handling pets, and after gardening or other contact with soil. HIV-infected persons should avoid sexual practices that might result in oral exposure to feces (e.g., oral-anal contact) (rating: BIII).
3. HIV-infected persons should be advised that newborn and very young pets might pose a small risk for transmitting cryptosporidial infection, but they should not be advised to destroy or give away healthy pets. Persons contemplating the acquisition of a new pet should avoid bringing any animal that has diarrhea into their households, should avoid purchasing a dog or cat aged less than 6 months, and should not adopt stray pets. HIV-infected persons who wish to assume the small risk for acquiring a puppy or kitten aged less than 6 months should request that their veterinarian examine the animal's stool for Cryptosporidium before they have contact with the animal (rating: BIII).
4. HIV-infected persons should avoid exposure to calves and lambs and to premises where these animals are raised (rating: BII).
5. HIV-infected persons should not drink water directly from lakes or rivers (rating: AIII).
6. Waterborne infection also might result from swallowing water during recreational activities. HIV-infected persons should be aware that many lakes, rivers, and salt-water beaches and some swimming pools, recreational water parks, and ornamental water fountains might be contaminated with human or animal waste that contains Cryptosporidium. They should avoid swimming in water that is likely to be contaminated and should avoid swallowing water while swimming or playing in recreational waters (rating: BIII).

7. Several outbreaks of cryptosporidiosis have been linked to municipal water supplies. During outbreaks or in other situations in which a community "boil-water" advisory is issued, boiling water for 1 minute will eliminate the risk for cryptosporidiosis (rating: AI). Use of submicron personal-use water filters* (home/office types) and/or bottled water** also might reduce the risk (rating: CIII). The magnitude of the risk for acquiring cryptosporidiosis from drinking water in a nonoutbreak setting is uncertain, and current data are inadequate to recommend that all HIV-infected persons boil water or avoid drinking tap water in nonoutbreak settings. However, HIV-infected persons who wish to take independent action to reduce the risk for waterborne cryptosporidiosis may choose to take precautions similar to those recommended during outbreaks. Such decisions should be made in conjunction with healthcare providers. Persons who opt for a personal-use filter or bottled water should be aware of the complexities involved in selecting appropriate products, the lack of enforceable standards for the destruction or removal of oocysts, the cost of the products, and the logistic difficulty of using these products consistently.

*Note: Only filters capable of removing particles 1 micrometer in diameter should be considered. Filters that provide the greatest assurance of oocyst removal include those that operate by reverse osmosis, those labeled as absolute 1-micrometer filters, and those labeled as meeting National Sanitations Foundation Standard No. 53 for cyst removal. The nominal 1-micrometer filter rating is not standardized, and many filters in this category might not be capable of removing 99% of the oocysts.

**Note: Sources of bottled water (e.g., wells, springs, municipal tap-water supplies, rivers, and lakes) and methods for its disinfection differ; therefore, all brands should both be presumed to be free of cryptosporidial oocysts than water from rivers or lakes. Water from wells and springs is much less likely to be contaminated by oocysts than water from rivers or lakes. Treatment of bottled water by distillation or reverse osmosis ensures oocyst removal. Water passed through an absolute 1-micrometer filter or a filter labeled as meeting National Sanitations Foundation Standard No. 53 for cyst removal before bottling will provide nearly the same level of protection. Use of nominal 1-micrometer filters by bottlers as the only barrier to Cryptosporidia might not result in removal of 99% of oocysts.

8. Patients who take precautions to avoid acquiring cryptosporidiosis from drinking water should be advised that ice made from contaminated tap water can also be a source of infection (rating: BII). Such persons also should be aware that fountain beverages served in restaurants, bars, theaters, and other places also might pose a risk because these beverages, as well as the ice they contain, are made from tap water. Nationally distributed brands of bottled or canned carbonated soft drinks are safe to drink. Commercially packaged noncarbonated soft drinks and fruit juices that do not require refrigeration until after they are opened (i.e., those that can be stored unrefrigerated on grocery shelves) also are safe. Nationally distributed brands of frozen fruit juice concentrate are safe if they are reconstituted by the user with water from a safe source. Fruit juices that must be kept refrigerated from the time they are processed to the time of consumption might be either fresh (unpasteurized) or heat-treated (pasteurized); only those juices labeled

as pasteurized should be considered free of risk from Cryptosporidium. Other pasteurized beverages and beers also are considered safe to drink (rating: BII). No data are available concerning survival of Cryptosporidium oocysts in wine.

9. HIV-infected persons should avoid eating raw oysters because cryptosporidial oocysts can survive in oysters for more than 2 months and have been found in oysters taken from some commercial oyster beds (rating: BIII). Cryptosporidium-infected patients should not work as food handlers, especially if the food to be handled is intended to be eaten without cooking (rating: BII). Because most foodborne outbreaks of cryptosporidiosis are believed to have been caused by infected food handlers, more specific recommendations to avoid exposure to contaminated food cannot be made.
10. In a hospital, standard precautions (i.e., use of gloves and hand washing after removal of gloves) should be sufficient to prevent transmission of cryptosporidiosis from an infected patient to a susceptible HIV-infected person (rating: BII). However, because of the potential for fomite transmission, some experts recommend that HIV-infected persons, especially those who are severely immunocompromised, should not share a room with a patient with cryptosporidiosis (rating: CIII).

Prevention of Disease

11. Rifabutin or clarithromycin, when taken for Mycobacterium avium complex prophylaxis, have been found to protect against cryptosporidiosis (Holmberg et al, 1998; Fichtenbaum et al, 2000). However, data are insufficient at this time to warrant a recommendation for using these drugs as chemoprophylaxis for cryptosporidiosis.

Prevention of Recurrence

12. No drug regimens are known to be effective in preventing the recurrence of cryptosporidiosis.

Special Considerations

Children

13. At present, no data indicate that formula-preparation practices for infants should be altered in an effort to prevent cryptosporidiosis (rating: CIII). However, in the event of a "boil-water" advisory, similar precautions for the preparation of infant formula should be taken as for drinking water for adults (rating: AII).

Microsporidiosis

Prevention of Exposure

1. Other than general attention to hand washing and other personal hygiene measures, no precautions to reduce exposure can be recommended at this time.

Prevention of Disease

2. No chemoprophylactic regimens are known to be effective in preventing microsporidiosis.

Prevention of Recurrence

3. No chemotherapeutic regimens are known to be effective in preventing the recurrence of microsporidiosis.

Tuberculosis

Prevention of Exposure

1. HIV-infected persons should be advised that certain activities and occupations might increase the likelihood of exposure to tuberculosis (rating: BIII). These include volunteer work or employment in health-care facilities, correctional institutions, and shelters for the homeless, as well as in other settings identified as high risk by local health authorities. Decisions about whether to continue with activities in these settings should be made in conjunction with the healthcare provider and should be based on factors such as the patient's specific duties in the workplace, the prevalence of tuberculosis in the community, and the degree to which precautions are taken to prevent the transmission of tuberculosis in the workplace (rating: BIII). Whether the patient continues with such activities might affect the frequency with which screening for tuberculosis needs to be conducted.

Prevention of Disease

2. When HIV infection is first recognized, the patient should receive a tuberculin skin test (TST) by administration of intermediate-strength (5-TU) purified protein derivative (PPD) by the Mantoux method (rating: AI). Routine evaluation for anergy is not recommended. However, there are selected situations in which anergy evaluation might assist in guiding individual decisions about preventive therapy (CDC, 2000; CDC, 1998).
3. All HIV-infected persons who have a positive tuberculin skin test result (greater than or equal to 5 mm of induration) should undergo chest radiography and clinical evaluation to rule out active tuberculosis. HIV-infected persons who have symptoms suggestive of tuberculosis should promptly undergo chest radiography and clinical evaluation regardless of their tuberculin skin test status (rating: AII).
4. All HIV-infected persons, regardless of age, who have a positive tuberculin skin test result yet have no evidence of active tuberculosis and no history of treatment for active or latent tuberculosis should be treated for latent tuberculosis infection. Options include isoniazid daily (rating: AII) or twice weekly (rating: BII) for 9 months; 4 months of therapy daily with either rifampin (rating: BIII) or rifabutin (rating: CIII); or 2 months of therapy with either rifampin and pyrazinamide* (see note below) (rating: BI) or rifabutin and pyrazinamide (rating: CIII) (CDC, 2000; CDC, 1998; Centers for Disease Control and Prevention, 2000). There have been reports of fatal and severe liver injury associated with the treatment of latent tuberculosis infection in HIV-uninfected persons treated with the 2 month regimen of daily

rifampin and pyrazinamide; therefore it may be prudent to use regimens that do not contain pyrazinamide in HIV-infected persons whose completion of treatment can be assured (Centers for Disease Control and Prevention [CDC]. Update: Fatal and Severe Liver Injuries Associated with Rifampin and Pyrazinamide for Latent Tuberculosis Infection and Revisions in American Thoracic Society/CDC Recommendations, United States 2001 MMWR Morb Mortal Wkly Rep 2001 Aug 31;50[34]:733-5). Because HIV-infected persons are at risk for peripheral neuropathy, those receiving isoniazid should also receive pyridoxine (rating: BIII). A decision to use a regimen containing either rifampin or rifabutin should be made after careful consideration of potential drug interactions, especially those related to protease inhibitors and nonnucleoside reverse transcriptase inhibitors (see the section/subsection titled "Special Considerations/Drug Interactions," below). Directly observed therapy should be used with intermittent dosing regimens (rating: AI) and when otherwise operationally feasible (rating: BIII) (CDC, 1998).

*Note from the National Guideline Clearinghouse (NGC): On August 11, 2003, the U.S. Food and Drug Administration, through its MedWatch program, distributed important safety information from the Centers for Disease Control and Prevention (CDC). The CDC notified healthcare professionals of revised recommendations against the use of rifampin plus pyrazinamide for treatment of latent tuberculosis infection, due to high rates of hospitalization and death from liver injury associated with the combined use of these drugs. For more information on this MedWatch alert, please see the U.S. Food and Drug Administration Center for Drug Evaluation and Research (CDER) Web site.

5. HIV-infected persons who are close contacts of persons who have infectious tuberculosis should be administered preventive therapy -- regardless of their tuberculin skin test results, age, or prior courses of chemoprophylaxis -- after the diagnosis of active tuberculosis has been excluded (rating: AII) (CDC, 2000; CDC, 1998; Centers for Disease Control and Prevention, 2000). In addition to household contacts, such persons might also include contacts in the same drug-treatment or healthcare facility, coworkers, and other contacts if transmission of tuberculosis is demonstrated.
6. For persons exposed to isoniazid- and/or rifampin-resistant tuberculosis, the decision to use chemoprophylactic antimycobacterial agents other than isoniazid alone, rifampin or rifabutin alone, rifampin plus pyrazinamide, or rifabutin plus pyrazinamide should be based on the relative risk for exposure to resistant organisms and should be made in consultation with public health authorities (rating: AII).
7. Tuberculin skin test-negative, HIV-infected persons from risk groups or geographic areas with a high prevalence of Mycobacterium tuberculosis infection might be at increased risk for primary or reactivation tuberculosis. However, the efficacy of preventive therapy in this group has not been demonstrated. Decisions concerning the use of chemoprophylaxis in these situations must be considered individually.
8. Although the reliability of the tuberculin skin test might diminish as the CD4+ T-lymphocyte count declines, annual repeat testing should be considered for HIV-infected persons who are tuberculin skin test-negative on initial evaluation and who belong to populations in which there is a substantial risk for exposure to Mycobacterium tuberculosis (rating: BIII). Clinicians should consider repeating the tuberculin skin test for persons whose initial skin test

was negative and whose immune function has improved in response to highly active antiretroviral therapies (i.e., those whose CD4+ T-lymphocyte count has increased to greater than 200 cells/microliter) (rating: BIII) (CDC, 2000). In addition to confirming tuberculosis infection, tuberculin skin test conversion in an HIV-infected person should alert healthcare providers to the possibility of recent Mycobacterium tuberculosis transmission and should prompt notification of public health officials for investigation to identify a possible source case.

9. The administration of Bacille Calmette-Guerin (BCG) vaccine to HIV-infected persons is contraindicated because of its potential to cause disseminated disease (rating: EII).

Prevention of Recurrence

10. Chronic suppressive therapy for a patient who has successfully completed a recommended regimen of treatment for tuberculosis is not necessary (rating: DII).

Special Considerations

Drug Interactions

11. Rifampin can induce metabolism of all the protease inhibitors and nonnucleoside reverse transcriptase inhibitors. This can result in more rapid drug clearance and possibly subtherapeutic drug concentrations of most of these antiretroviral agents. Rifampin should not be co-administered with the following protease inhibitors and nonnucleoside reverse transcriptase inhibitors: amprenavir, indinavir, lopinavir/ritonavir, nelfinavir, saquinavir, and delavirdine (CDC, 1998). However, it may be used with ritonavir, ritonavir plus saquinavir, efavirenz, and possibly with nevirapine. Rifabutin is an acceptable alternative to rifampin but should not be used with the protease inhibitor hard-gel saquinavir or delavirdine; caution is advised if the drug is coadministered with soft-gel saquinavir, because data are sparse. Rifabutin can be administered at one-half the usual daily dose, i.e., reduce from 300 mg to 150 mg per day, with indinavir, nelfinavir, or amprenavir or with one-fourth the usual dose, i.e., 150 mg every other day or three times a week, with ritonavir, ritonavir plus saquinavir, or lopinavir/ritonavir. When rifabutin is administered with indinavir as the sole protease inhibitor, the dose of indinavir should be increased from 800 mg every eight hours to 1,000 mg every eight hours. Pharmacokinetic data suggest that rifabutin at an increased dose can be administered with efavirenz; doses of 450 to 600 mg per day have been suggested (CDC, 2000). However, little information is available about appropriate dosing if a protease inhibitor is used concurrently with efavirenz and rifabutin; with such a combination the rifabutin dose might need to be reduced. Rifabutin can be used without dose adjustment with nevirapine.

Children

12. Infants born to HIV-infected mothers should have a tuberculin skin test (5-TU PPD) at or before the age of 9 to 12 months and should be retested at least once a year (rating: AIII). HIV-infected children living in households with

tuberculin skin test-positive persons should be evaluated for tuberculosis (rating: AIII); children exposed to a person who has active tuberculosis should be administered preventive therapy after active tuberculosis has been excluded, regardless of their tuberculin skin test results (rating: AII).

Pregnant Women

13. Chemoprophylaxis for tuberculosis is recommended during pregnancy for HIV-infected patients who have either a positive tuberculin skin test or a history of exposure to active tuberculosis, after active tuberculosis has been excluded (rating: AIII). A chest radiograph should be obtained before treatment and appropriate abdominal/pelvic lead apron shields should be used to minimize radiation exposure to the embryo/fetus. When an HIV-infected person has not been exposed to drug-resistant tuberculosis, isoniazid daily or twice weekly is the prophylactic regimen of choice. Because of concerns regarding possible teratogenicity associated with drug exposures during the first trimester, providers may choose to initiate prophylaxis after the first trimester. Preventive therapy with isoniazid should be accompanied by pyridoxine to reduce the risk for neurotoxicity. Experience with rifampin or rifabutin during pregnancy is more limited, but anecdotal experience with rifampin has not been associated with adverse pregnancy outcomes. Pyrazinamide should generally be avoided, particularly in the first trimester because of lack of information concerning fetal effects.

Disseminated Infection with Mycobacterium avium Complex

Prevention of Exposure

1. Organisms of the Mycobacterium avium complex (MAC) are common in environmental sources such as food and water. Current information does not support specific recommendations regarding avoidance of exposure.

Prevention of Disease

Initiation of Primary Prophylaxis

2. Adults and adolescents who have HIV infection should receive chemoprophylaxis against disseminated Mycobacterium avium complex disease if they have a CD4+ T-lymphocyte count of less than 50 cells/microliter (rating: AI) (Masur & the Public Health Service Task Force on Prophylaxis and Therapy for Mycobacterium avium complex, 1993). Clarithromycin (Benson, 2000; Pierce et al, 1996) or azithromycin (Havlir et al, 1996) are the preferred prophylactic agents (rating: AI). The combination of clarithromycin and rifabutin is no more effective than clarithromycin alone for chemoprophylaxis and is associated with a higher rate of adverse effects than either drug alone; this combination should not be used (rating: EI) (Havlir et al, 1996). The combination of azithromycin with rifabutin is more effective than azithromycin alone; however, the additional cost, increased occurrence of adverse effects, potential for drug interactions, and absence of a difference in survival when compared with azithromycin alone do not warrant a routine recommendation for this regimen (rating: CI) (Havlir et al, 1996). In addition to their preventive activity for Mycobacterium avium

complex disease, clarithromycin and azithromycin each confer protection against respiratory bacterial infections (rating: BII). If clarithromycin or azithromycin cannot be tolerated, rifabutin is an alternative prophylactic agent for Mycobacterium avium complex disease (rating: BI) (Centers for Disease Control and Prevention, 2000). Tolerance, cost, and drug interactions are among the issues that should be considered in decisions regarding the choice of prophylactic agents for Mycobacterium avium complex disease. Particular attention to interactions with antiretroviral protease inhibitors and nonnucleoside reverse transcriptase inhibitors is warranted (see the section/subsection titled "Special Considerations/Drug Interactions," below). Before prophylaxis is initiated, disseminated Mycobacterium avium complex disease should be ruled out by clinical assessment, which might include obtaining a blood culture for Mycobacterium avium complex if warranted. Because treatment with rifabutin could result in the development of resistance to rifampin in persons who have active tuberculosis, active tuberculosis should also be excluded before rifabutin is used for prophylaxis.

3. Although the detection of Mycobacterium avium complex organisms in the respiratory or gastrointestinal tract might predict the development of disseminated Mycobacterium avium complex infection, no data are available on the efficacy of prophylaxis with clarithromycin, azithromycin, rifabutin, or other drugs in patients with Mycobacterium avium complex organisms at these sites and a negative blood culture. Therefore, routine screening of respiratory or gastrointestinal specimens for Mycobacterium avium complex cannot be recommended (rating: DIII).

Discontinuation of Primary Prophylaxis

4. Primary Mycobacterium avium complex prophylaxis should be discontinued in adult and adolescent patients who have responded to highly active antiretroviral therapies with an increase in CD4+ T lymphocyte count to >100 cells/microliter for at least 3 months (rating: AI). Two large randomized, placebo controlled trials and observational data have shown that such patients can discontinue primary prophylaxis with minimal risk of developing Mycobacterium avium complex (Dworkin et al, 2000; El-Sadr et al, 2000; Currier et al, 2000; Furrer et al, 2000). Discontinuation of primary prophylaxis in patients meeting the criteria above is recommended not only because prophylaxis appears to add very little to disease prevention for Mycobacterium avium complex or for bacterial infections, but also because discontinuation of drug reduces pill burden, the potential for drug toxicity, drug interactions, selection of drug resistant pathogens, and cost.

Restarting Primary Prophylaxis

5. Primary prophylaxis should be reintroduced if the CD4+ T lymphocyte count decreases to <50 to 100 cells/microliter (rating: AIII).

Prevention of Recurrence

6. Adult and adolescent patients with disseminated Mycobacterium avium complex should receive lifelong therapy (i.e., secondary prophylaxis or maintenance therapy) (rating: AII), unless immune reconstitution occurs as a consequence of highly active antiretroviral therapies (see Recommendation

No. 7, below). Unless good clinical or laboratory evidence of macrolide resistance exists, the use of a macrolide (clarithromycin or, alternatively, azithromycin) is recommended in combination with ethambutol (rating: AII) with or without rifabutin (rating: CI) (Gordin et al, 1999; Benson et al, 1999). Treatment of Mycobacterium avium complex disease with clarithromycin in a dose of 1,000 mg twice a day is associated with a higher mortality rate than has been observed with clarithromycin administered at 500 mg twice a day; thus, the higher dose should not be used (rating: EI) (Chaisson, et al, 1994; Cohn et al, 1999). Clofazimine has been associated with adverse clinical outcomes in the treatment of Mycobacterium avium complex disease and should not be used (rating: DII) (Chaisson et al, 1997).

Discontinuation of Secondary Prophylaxis (Chronic Maintenance Therapy)

7. Patients appear to be at low risk for recurrence of Mycobacterium avium complex when they have completed a course of at least 12 months of treatment for Mycobacterium avium complex, remain asymptomatic with respect to Mycobacterium avium complex signs and symptoms, and have a sustained increase, e.g., $\geq$6 months, in their CD4+ T-lymphocyte counts to >100 cells/microliter following highly active antiretroviral therapies. While the numbers of patients who have been evaluated remain small, and recurrences could occur (Kirk et al, 1999; Soriano et al, 2000; Rabaud et al, 2000; Aberg, Yijko, & Jacobson, 1998; Shafran et al, 2001), based on these observations and on inference from more extensive data suggesting the safety of discontinuation of secondary prophylaxis for other opportunistic infections during advanced HIV disease, it may be reasonable to consider discontinuation of chronic maintenance therapy in such patients (rating: CIII). Some experts would obtain a blood culture for Mycobacterium avium complex, even in asymptomatic patients, prior to discontinuation of therapy, to substantiate that disease is no longer active.

Restarting Secondary Prophylaxis

8. Secondary prophylaxis should be reintroduced if the CD4+ T lymphocyte count decreases to <100 cells/microliter (rating: AIII).

Special Considerations

Drug Interactions

9. Rifabutin should not be administered to patients receiving certain protease inhibitors and nonnucleoside reverse transcriptase inhibitors because the complex interactions have been incompletely studied, and the clinical implications of those interactions are unclear (USPHS/IDSA Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents, date not given; Centers for Disease Control and Prevention, 2000) (see the section/subsection titled "Special Considerations/Drug Interactions" in the information provided under "Tuberculosis," above). Protease inhibitors may increase clarithromycin levels, but no recommendation to adjust the dose of either clarithromycin or protease inhibitors can be made on the basis of existing data. Efavirenz can induce metabolism of clarithromycin. This may result in reduced serum concentration of clarithromycin but increased

concentration of 14-OH clarithromycin, an active metabolite of clarithromycin. Although the clinical significance of this interaction is not known, the efficacy of clarithromycin in Mycobacterium avium complex prophylaxis could be reduced because of this interaction. Azithromycin pharmacokinetics are not affected by the cytochrome P450 system; azithromycin can be used safely in the presence of protease inhibitors and/or nonnucleoside reverse transcriptase inhibitors without concerns of drug interactions.

Children

10. HIV-infected children aged younger than 13 years who have advanced immunosuppression also can develop disseminated Mycobacterium avium complex infections, and prophylaxis should be offered to high-risk children according to the following CD4+ T-lymphocyte thresholds: children aged 6 years and older, less than 50 cells/microliter; children aged 2 to 6 years, less than 75 cells/microliter; children aged 1 to 2 years, less than 500 cells/microliter; and children aged younger than 12 months, less than 750 cells/microliter (rating: AII). For the same reasons that clarithromycin and azithromycin are the preferred prophylactic agents for adults, they should also be considered for children (rating: AII); oral suspensions of both agents are commercially available in the United States. No liquid formulation of rifabutin suitable for pediatric use is commercially available in the United States. Children with a history of disseminated Mycobacterium avium complex should be administered lifelong prophylaxis to prevent recurrence (rating: AII). The safety of discontinuing Mycobacterium avium complex prophylaxis in children whose CD4+ T-lymphocyte counts have increased in response to highly active retroviral therapies has not been studied.

Pregnant Women

11. Chemoprophylaxis for Mycobacterium avium complex disease should be administered to pregnant women as is done for other adults and adolescents (rating: AIII). However, because of general concerns about administering drugs during the first trimester of pregnancy, some providers may choose to withhold prophylaxis during the first trimester. Animal studies and anecdotal evidence of safety in humans suggest that of the available agents, azithromycin is the drug of choice (rating: BIII) (Adair et al, 1998). Experience with rifabutin is limited. Clarithromycin has been demonstrated to be a teratogen in animals and should be used with caution during pregnancy (Medical Economics Company, Inc., 2001). For secondary prophylaxis (chronic maintenance therapy), azithromycin plus ethambutol are the preferred drugs (rating: BIII) (Adair et al,1998).

<u>Bacterial Respiratory Infections</u>

Prevention of Exposure

1. Because Streptococcus pneumoniae and Haemophilus influenzae are common in the community, no effective way exists to reduce patient exposure to these bacteria.

Prevention of Disease

2. Adults and adolescents who have a CD4+ T-lymphocyte count of greater than or equal to 200 cells/microliter should be administered a single dose of 23-valent polysaccharide pneumococcal vaccine if they have not received this vaccine during the previous five years (rating: BII) (Dworkin, 2001; Guerrero et al, 1999; Gebo et al, 1996; CDC, 1997; Breiman, Keller, & Phelan, 2000). One randomized placebo-controlled trial of pneumococcal vaccine in Africa paradoxically found an increase in pneumonia among vaccinated subjects (French et al, 2000). However, several observational studies in the United States have not identified increased risk associated with vaccination and have identified benefit in this group (Dworkin, 2001; Guerrero et al, 1999; Gebo et al, 1996; CDC, 1997; Breiman, Keller, & Phelan, 2000). Most experts believe that the potential benefit of pneumococcal vaccination in the United States outweighs the risk. Immunization should also be considered for patients with CD4+ T lymphocyte counts <200 cells/microliter, although there is no clinical evidence for efficacy (rating: CIII). Revaccination may be considered for patients who were initially immunized when their CD4+ T lymphocyte count was <200 cells/microliter and whose CD4+ count has increased to >200 cells/microliter in response to highly active antiretroviral therapies (rating: CIII). The recommendation to vaccinate is increasingly pertinent because of the increasing incidence of invasive infections with drug-resistant (including trimethoprim-sulfamethoxazole-, macrolide-, and beta-lactam-resistant) strains of Streptococcus pneumoniae.
3. The duration of the protective effect of primary pneumococcal vaccination is unknown. Periodic revaccination may be considered; an interval of 5 years has been recommended for persons not infected with HIV and also might be appropriate for persons infected with HIV (rating: CIII). There is, however, no evidence for clinical benefit from revaccination.
4. The incidence of Haemophilus influenzae type B infection in adults is low. Therefore, Haemophilus influenzae type B vaccine is not generally recommended for adult use (rating: DIII).
5. Trimethoprim-sulfamethoxazole, when administered daily for Pneumocystis carinii pneumonia prophylaxis, reduces the frequency of bacterial respiratory infections; this should be considered in the selection of an agent for Pneumocystis carinii pneumonia prophylaxis (rating: AII). However, indiscriminate use of this drug (when not indicated for Pneumocystis carinii pneumonia prophylaxis or other specific reasons) might promote the development of trimethoprim-sulfamethoxazole-resistant organisms. Thus, trimethoprim-sulfamethoxazole should not be prescribed solely to prevent bacterial respiratory infection (rating: DIII). Similarly, clarithromycin administered daily and azithromycin administered weekly for Mycobacterium avium complex prophylaxis might be effective in preventing bacterial respiratory infections; this should be considered in the selection of an agent for prophylaxis against Mycobacterium avium complex disease (rating: BII). However, these drugs should not be prescribed solely for preventing bacterial respiratory infection (rating: DIII).
6. An absolute neutrophil count that is depressed because of HIV disease or drug therapy is associated with an increased risk for bacterial infections, including pneumonia. To reduce the risk for such bacterial infections, providers may consider taking steps to reverse neutropenia, either by stopping myelosuppressive drugs (rating: CII) or by administering granulocyte-colony-stimulating factor (G-CSF) (rating: CII).

Prevention of Recurrence

7. Some clinicians may administer antibiotic chemoprophylaxis to HIV-infected patients who have very frequent recurrences of serious bacterial respiratory infections (rating: CIII). Trimethoprim-sulfamethoxazole, administered for Pneumocystis carinii pneumonia prophylaxis, and clarithromycin or azithromycin, administered for Mycobacterium avium complex prophylaxis, are appropriate for drug-sensitive organisms. However, providers should be cautious about using antibiotics solely for preventing the recurrence of serious bacterial respiratory infections because of the potential development of drug-resistant microorganisms and drug toxicity.

Special Considerations

Children

8. HIV infected children, less than five years old should be administered Haemophilus influenzae type b vaccine (rating: AII) and pneumococcal conjugate vaccine (Centers for Disease Control and Prevention, 2001; American Academy of Pediatrics, 2000; CDC, 2000) (rating: BII) in accordance with the guidelines of the Advisory Committee on Immunization Practices (Guerrero et al, 1999; CDC, 1997; Centers for Disease Control and Prevention, 2001) and the American Academy of Pediatrics (2000) Recommendations for the prevention of pneumococcal infections, including the use of pneumococcal conjugate vaccine (Prevnar), pneumococcal polysaccharide vaccine, and antibiotic prophylaxis. Pediatrics 2000;106[2 Pt 1]:362-6). Children aged greater than 2 years should also receive the 23-valent polysaccharide pneumococcal vaccine (rating: BII). Revaccination with a second dose of the 23 valent polysaccharide pneumococcal vaccine should generally be offered after 3 to 5 years to children aged 10 years or younger and after 5 years to children older than 10 years (rating: BIII).

   Notice from the National Guideline Clearinghouse (NGC) and the Centers for Disease Control and Prevention: On March 2, 2004, the Centers for Disease Control and Prevention (CDC), the American Academy of Pediatrics (AAP), and the American Academy of Family Physicians (AAFP), issued temporary recommendations to suspend routine use of both the third and fourth doses of pneumococcal conjugate vaccine (PCV7; Prevnar®). Children at increased risk of severe disease should continue to receive the full, routine, four-dose series. The recommendations were issued in response to a low vaccine supply. For more information, refer to the CDC Web site.

9. To prevent serious bacterial infections in HIV-infected children who have hypogammaglobulinemia (immunoglobulin G less than 400 mg/dL), clinicians should use intravenous immunoglobulin (IVIG) (rating: AI). Respiratory syncytial virus (RSV) intravenous immunoglobulin (750 mg/kg), not monoclonal respiratory syncytial virus antibody, may be substituted for intravenous immunoglobulin during the respiratory syncytial virus season to provide broad anti-infective protection, if respiratory syncytial virus intravenous immunoglobulin is available.
10. To prevent recurrence of serious bacterial respiratory infections, antibiotic chemoprophylaxis may be considered (rating: BI). However, providers should be cautious about using antibiotics solely for this purpose because of the potential development of drug-resistant microorganisms and drug toxicity.

The administration of intravenous immunoglobulin should also be considered for HIV-infected children who have recurrent serious bacterial infections (rating: BI), although such treatment might not provide additional benefit to children who are being administered daily trimethoprim-sulfamethoxazole. However, intravenous immunoglobulin may be considered for children who have recurrent serious bacterial infections despite receiving trimethoprim-sulfamethoxazole or other antimicrobials (rating: CIII) (Spector et al, 1994).

Pregnant Women

11. Pneumococcal vaccination is recommended during pregnancy for HIV-infected patients who have not been vaccinated during the previous 5 years (rating: BIII). Among nonpregnant adults, vaccination has been associated with a transient burst of HIV replication. Whether the transient viremia can increase the risk for perinatal HIV transmission is unknown. Because of this concern, when feasible, vaccination may be deferred until after antiretroviral therapy has been initiated to prevent perinatal HIV transmission (rating: CIII).

Bacterial Enteric Infections

Prevention of Exposure

Food

1. Health-care providers should advise HIV-infected persons not to eat raw or undercooked eggs (including foods that might contain raw eggs [e.g., some preparations of hollandaise sauce, Caesar and other salad dressings, some mayonnaises, uncooked cookie and cake batter, egg nog]); raw or undercooked poultry, meat, or seafood (especially raw shellfish); unpasteurized dairy products; unpasteurized fruit juices; and raw seed sprouts (e.g., alfalfa sprouts, mung bean sprouts). Poultry and meat are safest when adequate cooking is confirmed with a thermometer (internal temperature of 180 degrees F for poultry and degrees 165 degrees F for red meats). If a thermometer is not used, the risk of illness is decreased by consuming poultry and meat that have no trace of pink color. Color change of the meat (e.g., absence of pink) does not always correlate with internal temperature. (rating: BIII). Produce should be washed thoroughly before being eaten (rating: BIII).
2. Healthcare providers should advise HIV-infected persons to avoid cross-contamination of foods. Uncooked meats (including hot dogs) and their juices should not come into contact with other foods. Hands, cutting boards, counters, knives, and other utensils should be washed thoroughly after contact with uncooked foods (rating: BIII).
3. Healthcare providers should advise HIV-infected persons that, although the incidence of listeriosis is low, it is a serious disease that occurs with unusually high frequency among severely immunosuppressed HIV-infected persons. An immunosuppressed, HIV-infected person who wishes to reduce the risk of acquiring listeriosis as much as possible may choose to do the following (rating: CIII): (a) avoid soft cheeses (e.g., feta, Brie, Camembert, blue-veined and Mexican-style cheese such as queso fresco). Hard cheeses, processed cheeses, cream cheese (including slices and spreads), cottage cheese, or yogurt need not be avoided; (b) cook leftover foods or ready-to-

eat foods (e.g., hot dogs) until steaming hot before eating; (c) avoid foods from delicatessen counters (e.g., prepared salads, meats, cheeses) or heat/reheat these foods until steaming before eating; (d) avoid refrigerated pates and other meat spreads, or heat/reheat these foods until steaming. Canned or shelf-stable pate and meat spreads need not be avoided; (e) avoid raw or unpasteurized milk (including goat's milk) or milk-products, or foods which contain unpasteurized milk or milk-products. (rating: CIII).

Pets

4. When obtaining a new pet, HIV-infected persons should avoid animals aged younger than 6 months, especially those that have diarrhea (rating: BIII).
5. HIV-infected persons should avoid contact with animals that have diarrhea (rating: BIII). HIV-infected pet owners should seek veterinary care for animals with diarrheal illness, and a fecal sample from such animals should be examined for Cryptosporidium, Salmonella, and Campylobacter.
6. HIV-infected persons should wash their hands after handling pets (especially before eating) and should avoid contact with pets' feces (rating: BIII).
7. HIV-infected persons should avoid contact with reptiles (e.g., snakes, lizards, iguanas, and turtles) because of the risk for salmonellosis (rating: BIII).

Travel

8. The risk for foodborne and waterborne infections among immunosuppressed, HIV-infected persons is magnified during travel to developing countries. Persons who travel to such countries should avoid foods and beverages that might be contaminated, particularly raw fruits and vegetables, raw or undercooked seafood or meat, tap water, ice made with tap water, unpasteurized milk and dairy products, and items sold by street vendors (rating: AII). Foods and beverages that are generally safe include steaming-hot foods, fruits that are peeled by the traveler, bottled (especially carbonated) beverages, hot coffee and tea, beer, wine, and water brought to a rolling boil for 1 minute (rating: AII). Treatment of water with iodine or chlorine might not be as effective as boiling but can be used when boiling is not practical (rating: BIII).

Prevention of Disease

9. Prophylactic antimicrobial agents are not generally recommended for travelers (rating: DIII). The effectiveness of these agents depends on local antimicrobial-resistance patterns of gastrointestinal pathogens, which are seldom known. Moreover, these agents can elicit adverse reactions and can promote the emergence of resistant organisms. However, for HIV-infected travelers, antimicrobial prophylaxis may be considered, depending on the level of immunosuppression and the region and duration of travel (rating: CIII). The use of fluoroquinolones such as ciprofloxacin (500 mg per day) can be considered when prophylaxis is deemed necessary (rating: BIII). As an alternative (e.g., for children, pregnant women, and persons already taking trimethoprim-sulfamethoxazole for Pneumocystis carinii pneumonia prophylaxis), trimethoprim-sulfamethoxazole might offer some protection against traveler's diarrhea (rating: BIII). The risk of toxicity should be

considered before treatment with trimethoprim-sulfamethoxazole is initiated solely because of travel.

10. Antimicrobial agents such as fluoroquinolones should be given to patients before their departure, to be taken empirically (e.g., 500 mg of ciprofloxacin twice a day for 3 to 7 days) should traveler's diarrhea develop (rating: BIII). Fluoroquinolones should be avoided for children aged less than 18 years and pregnant women, and alternative antibiotics should be considered (rating: BIII). Travelers should consult a physician if their diarrhea is severe and does not respond to empirical therapy, if their stools contain blood, if fever is accompanied by shaking chills, or if dehydration develops. Antiperistaltic agents (e.g., diphenoxylate and loperamide) can be used to treat mild diarrhea. However, the use of these drugs should be discontinued if symptoms persist beyond 48 hours. Moreover, these agents should not be administered to patients who have a high fever or who have blood in the stool (rating: AII).
11. Some experts recommend that HIV-infected persons who have Salmonella gastroenteritis be administered antimicrobial therapy to prevent extraintestinal spread of the pathogen. However, no controlled study has demonstrated a beneficial effect of such treatment, and some studies of immunocompetent persons have suggested that antimicrobial therapy can lengthen the shedding period. The fluoroquinolones -- primarily ciprofloxacin (750 mg twice a day for 14 days) -- can be used when antimicrobial therapy is chosen (rating: CIII).

Prevention of Recurrence

12. HIV-infected persons who have Salmonella septicemia require long-term therapy (i.e., secondary prophylaxis or chronic maintenance therapy) to prevent recurrence. Fluoroquinolones, primarily ciprofloxacin, are usually the drugs of choice for susceptible organisms (rating: BII).
13. Household contacts of HIV-infected persons who have salmonellosis or shigellosis should be evaluated for persistent asymptomatic carriage of Salmonella or Shigella so that strict hygienic measures and/or antimicrobial therapy can be instituted and recurrent transmission to the HIV-infected person can be prevented (rating: CIII).

Special Considerations

Children

14. Like HIV-infected adults, HIV-infected children should wash their hands after handling pets (especially before eating) and should avoid contact with pets' feces. Hand washing should be supervised (rating: BIII).
15. HIV-exposed infants aged younger than 3 months and all HIV-infected children who have severe immunosuppression should be administered treatment for Salmonella gastroenteritis to prevent extraintestinal spread of the pathogen (rating: CIII). Choices of antibiotics include trimethoprim-sulfamethoxazole, ampicillin, cefotaxime, ceftriaxone, or chloramphenicol; fluoroquinolones should be used with caution and only if no alternatives exist.
16. HIV-infected children who have Salmonella septicemia should be offered long-term therapy to prevent recurrence (rating: CIII). Trimethoprim-sulfamethoxazole is the drug of choice; ampicillin or chloramphenicol can be

used if the organism is susceptible. Fluoroquinolones should be used with caution and only if no alternative exists.
17. Antiperistaltic drugs are not recommended for children (rating: DIII).

Pregnant Women

18. Because both pregnancy and HIV infection confer a risk for listeriosis, pregnant HIV-infected women should heed recommendations regarding listeriosis (rating: BII).
19. Because extraintestinal spread of Salmonella during pregnancy might lead to infection of the placenta and amniotic fluid and result in pregnancy loss similar to that seen with Listeria monocytogenes, pregnant women with Salmonella gastroenteritis should receive treatment (rating: BIII). Choices for treatment include ampicillin, cefotaxime, ceftriaxone, or trimethoprim-sulfamethoxazole. Fluoroquinolones should be avoided.
20. Fluoroquinolones should not be used during pregnancy. Trimethoprim-sulfamethoxazole might offer some protection against traveler's diarrhea.

Bartonellosis

Prevention of Exposure

1. HIV-infected persons, particularly those who are severely immunosuppressed, are at unusually high risk for developing relatively severe disease due to infection with Bartonella, which can be transmitted from cats. These persons should consider the potential risks of cat ownership (rating: CIII). Persons who acquire a cat should adopt or purchase an animal aged older than 1 year that is in good health (rating: BII).
2. Although declawing is not generally advised, HIV-infected persons should avoid rough play with cats and situations in which scratches are likely (rating: BII). Any cat-associated wounds should be washed promptly (rating: CIII). Cats should not be allowed to lick open wounds or cuts of HIV-infected persons (rating: BIII).
3. Care of cats should include flea control (rating: CIII).
4. No evidence indicates any benefits to cats or their owners from routine culture or serologic testing of the pet for Bartonella infection (rating: DII).

Prevention of Disease

5. No data support chemoprophylaxis for Bartonella-associated disease (rating: CIII).

Prevention of Recurrence

6. Relapse or reinfection with Bartonella has sometimes followed a course of primary treatment. Although no firm recommendation can be made regarding prophylaxis in this situation, long-term suppression of infection with erythromycin or doxycycline should be considered (rating: CIII).

Special Considerations

Children

7. The risks of cat ownership for HIV-infected children who are severely immunocompromised should be discussed with parents and caretakers (rating: CIII).

Pregnant Women

8. If long-term suppression of Bartonella infection is required, erythromycin should be used. Tetracyclines should not be used during pregnancy.

Candidiasis

Prevention of Exposure

1. Candida organisms are common on mucosal surfaces and skin. No measures are available to reduce exposure to these fungi.

Prevention of Disease

2. Data from prospective controlled trials indicate that fluconazole can reduce the risk for mucosal (oropharyngeal, esophageal, and vaginal) candidiasis and cryptococcosis as well in patients with advanced HIV disease (CDC, 1997; Breiman, Keller, & Phelan, 2000; French et al, 2000). However, routine primary prophylaxis is not recommended because of the effectiveness of therapy for acute disease, the low mortality associated with mucosal candidiasis, the potential for resistant Candida organisms to develop, the possibility of drug interactions, and the cost of prophylaxis (rating: DIII).

Prevention of Recurrence

3. Many experts do not recommend chronic prophylaxis of recurrent oropharyngeal or vulvovaginal candidiasis for the same reasons that they do not recommend primary prophylaxis. However, if recurrences are frequent or severe, providers may consider administering an oral azole (fluconazole [rating: CI] (Powderly et al, 1995; Schuman et al, 1997; Havlir et al, 1998) or itraconazole solution [rating: CI]). Other factors that influence choices about such therapy include the impact of the recurrences on the patient's well-being and quality of life, the need for prophylaxis for other fungal infections, cost, toxicities, drug interactions, and the potential to induce drug resistance among Candida and other fungi. Prolonged use of systemically absorbed azoles, particularly in patients with low CD4+ T-lymphocyte counts (i.e., less than 100 cells/microliter), increases the risk for the development of azole resistance.
4. Adults or adolescents who have a history of documented esophageal candidiasis, particularly multiple episodes, should be considered candidates for chronic suppressive therapy. Fluconazole at a dose of 100 to 200 mg daily is appropriate (rating: BI). However, the potential development of azole resistance should be taken into account when long-term azoles are considered.

Special Considerations

Children

5. Primary prophylaxis of candidiasis in HIV-infected infants is not indicated (rating: DIII).
6. Suppressive therapy with systemic azoles should be considered for infants who have severe recurrent mucocutaneous candidiasis (rating: CIII) and particularly for those who have esophageal candidiasis (rating: BIII).

Pregnant Women

7. Experience is limited with the use of systemic antifungal drugs during human pregnancy. Four cases of infants born with craniofacial and skeletal abnormalities following prolonged in utero exposure to fluconazole have been reported (Pursley et al, 1996; Aleck & Bartley, 1997). In addition, itraconazole is embryotoxic and teratogenic in animal systems (Janssen Pharmaceutical Company, 1999. These same potential risks of teratogenicity are presumed to apply to other systemically absorbed azole antifungals, such as ketoconazole. Therefore, chemoprophylaxis against oropharyngeal, esophageal, or vaginal candidiasis using systemically absorbed azoles should not be initiated during pregnancy (rating: DIII), and azoles should be discontinued for HIV-infected women who become pregnant (rating: DIII). Effective birth control measures should be recommended to all HIV-infected women on azole therapy for candidiasis (rating: AIII).

Cryptococcosis

Prevention of Exposure

1. HIV-infected persons cannot completely avoid exposure to Cryptococcus neoformans. No evidence exists that exposure to pigeon droppings is associated with an increased risk for acquiring cryptococcosis.

Prevention of Disease

2. Routine testing of asymptomatic persons for serum cryptococcal antigen is not recommended because of the low probability that the results will affect clinical decisions (rating: DIII).
3. Prospective controlled trials indicate that fluconazole and itraconazole can reduce the frequency of cryptococcal disease among patients who have advanced HIV disease. However, most experts recommend that antifungal prophylaxis not be used routinely to prevent cryptococcosis because of the relative infrequency of cryptococcal disease, the lack of survival benefits associated with prophylaxis, the possibility of drug interactions, the potential development of antifungal drug resistance, and cost. The need for prophylaxis or suppressive therapy for other fungal infections (e.g., candidiasis, histoplasmosis, or coccidioidomycosis) should be considered in making decisions about prophylaxis for cryptococcosis. If used, fluconazole at doses of 100 to 200 mg daily is reasonable for patients whose CD4+ T-lymphocyte counts are less than 50 cells/microliter (rating: CI) (Powderly et al, 1995).

Prevention of Recurrence

4. Patients who complete initial therapy for cryptococcosis should be administered lifelong suppressive treatment (i.e., secondary prophylaxis or chronic maintenance therapy) (rating: AI) unless immune reconstitution occurs as a consequence of highly active antiretroviral therapy (see Recommendation No. 5, below). Fluconazole is superior to itraconazole in preventing relapse of cryptococcal disease and is the preferred drug (rating: AI) (Bozzette et al, 1991; Powderly et al, 1992; Saag et al, 1999).

Discontinuation of Secondary Prophylaxis (Chronic Maintenance Therapy)

5. Adult and adolescent patients appear to be at low risk for recurrence of cryptococcosis when they have successfully completed a course of initial therapy for cryptococcosis, remain asymptomatic with respect to signs and symptoms of cryptococcosis, and have a sustained increase (e.g., 6 months) in their CD4+ T-lymphocyte counts to >100 to 200 cells/microliter following highly active antiretroviral therapies. The numbers of patients who have been evaluated remain small (Aberg et al, 2000; Mussini et al, 2001). Based on these observations and on inference from more extensive data suggesting the safety of discontinuation of secondary prophylaxis for other opportunistic infections during advanced HIV disease, and while recurrences could occur it may be reasonable to consider discontinuation of chronic maintenance therapy in such patients (rating: CIII). Some experts would perform a lumbar puncture to determine if the cerebrospinal fluid is culture negative before stopping therapy even if patients have been asymptomatic; other experts do not believe this is necessary.

Restarting Secondary Prophylaxis

6. Maintenance therapy should be reinitiated if the CD4+ T-lymphocyte count decreases to <100-200 cells/microliter (rating: AIII).

Special Considerations

Children

7. No data exist on which to base specific recommendations for children, but lifelong suppressive therapy with fluconazole after an episode of cryptococcosis is appropriate (rating: AII).

Pregnant Women

8. Prophylaxis with fluconazole or itraconazole should not be initiated during pregnancy because of the low incidence of cryptococcal disease, the lack of a recommendation for primary prophylaxis against cryptococcosis in nonpregnant adults, and potential teratogenic effects of these drugs during pregnancy (rating: DIII) (Pursley et al, 1996; Aleck & Bartley, 1997). For patients who conceive while being administered primary prophylaxis and who elect to continue their pregnancy, prophylaxis should be discontinued. The occurrence of craniofacial and skeletal abnormalities in infants following

prolonged in utero exposure to fluconazole should be considered when assessing the therapeutic options for HIV-infected women who become pregnant and are receiving secondary prophylaxis (chronic maintenance therapy) for cryptococcosis (Pursley et al, 1996; Aleck & Bartley, 1997). If a woman meets the criteria for discontinuation of secondary prophylaxis as discussed above, strong consideration should be given to discontinuing therapy during pregnancy as long as the CD4+ T lymphocyte could remains above 100 to 200 cells/microliter. For patients requiring therapy, amphotericin B may be preferred, especially during the first trimester. Effective birth control measures should be recommended to all HIV-infected women on azole therapy for cryptococcosis (rating: AIII).

Histoplasmosis

Prevention of Exposure

1. Although HIV-infected persons living in or visiting histoplasmosis-endemic areas cannot completely avoid exposure to Histoplasma capsulatum, those whose CD4+ T-lymphocyte counts are less than 200 cells/microliter should avoid activities known to be associated with increased risk (e.g., creating dust when working with surface soil; cleaning chicken coops that are heavily contaminated with droppings; disturbing soil beneath bird-roosting sites; cleaning, remodeling, or demolishing old buildings; and exploring caves) (rating: CIII).

Prevention of Disease

2. Routine skin testing with histoplasmin and serologic testing for antibody or antigen in histoplasmosis-endemic areas are not predictive of disease and should not be performed (rating: DII).
3. Data from a prospective randomized controlled trial indicate that itraconazole can reduce the frequency of histoplasmosis among patients who have advanced HIV infection and who live in Histoplasma capsulatum-endemic areas (McKinsey et al, 1999). However, no survival benefit was observed among persons receiving itraconazole. Prophylaxis with itraconazole may be considered in patients with CD4+ T-lymphocyte counts less than 100 cells/microliter who are at especially high risk because of occupational exposure or who live in a community with a hyperendemic rate of histoplasmosis (greater than or equal to 10 cases per 100 patient-years) (rating: CI).

Prevention of Recurrence

4. Patients who complete initial therapy for histoplasmosis should be administered lifelong suppressive treatment (i.e., secondary prophylaxis or chronic maintenance therapy) with itraconazole (200 mg twice a day) (rating: AI) (Wheat et al,1993).

Discontinuation of Secondary Prophylaxis (Chronic Maintenance Therapy)

5. Although patients receiving secondary prophylaxis (chronic maintenance therapy) might be at low risk for recurrence of systemic mycosis when their CD4+ T-lymphocyte counts increase to greater than 100 cells/microliter on highly active antiretroviral therapies, the numbers of patients who have been evaluated are insufficient to warrant a recommendation to discontinue prophylaxis.

Special Considerations

Children

6. Because primary histoplasmosis can lead to disseminated infection in children, a reasonable option is to administer lifelong suppressive therapy after an acute episode of the disease (rating: AIII).

Pregnant Women

7. Because of the embryotoxicity and teratogenicity of itraconazole in animal systems, primary prophylaxis against histoplasmosis should not be offered during pregnancy (rating: DIII) (CDC, 2000). These data as well as the observation of craniofacial and skeletal abnormalities in infants following prolonged in utero exposure to fluconazole (Pursley et al, 1996; Aleck & Bartley, 1997) should be considered when assessing the need for chronic maintenance therapy in HIV-infected pregnant women with histoplasmosis. For such patients, therapy with amphotericin B may be preferred, especially during the first trimester. For women receiving highly active antiretroviral therapies with a sustained rise in CD4+ T lymphocyte counts above 100 cells/microliter, discontinuation of azole prophylaxis, especially during the first trimester, should be considered. Effective birth control measures should be recommended to all HIV-infected women on azole therapy for histoplasmosis (rating: AIII).

Coccidioidomycosis

Prevention of Exposure

1. Although HIV-infected persons living in or visiting areas in which coccidioidomycosis is endemic cannot completely avoid exposure to Coccidioides immitis, they should, when possible, avoid activities associated with increased risk (e.g., those involving extensive exposure to disturbed native soil, for example, at building excavation sites or during dust storms) (rating: CIII).

Prevention of Disease

2. Routine skin testing with coccidioidin (spherulin) in coccidioidomycosis-endemic areas is not predictive of disease and should not be performed (rating: DII). Within the endemic area, a positive serologic test might indicate an increased risk for active infection; however, routine testing does not appear to be useful and should not be performed (rating: DIII).

3. Primary prophylaxis for HIV-infected persons who live in coccidioidomycosis-endemic areas is not routinely recommended.

Prevention of Recurrence

4. Patients who complete initial therapy for coccidioidomycosis should be administered lifelong suppressive therapy (i.e., secondary prophylaxis or chronic maintenance therapy) (rating: AII) using either 400 mg of fluconazole by mouth each day or 200 mg of itraconazole twice a day (Galgiani et al, 2000). Patients with meningeal disease require consultation with an expert.

Discontinuation of Secondary Prophylaxis (Chronic Maintenance Therapy)

5. Although patients receiving secondary prophylaxis (chronic maintenance therapy) might be at low risk for recurrence of systemic mycosis when their CD4+ T-lymphocyte counts increase to greater than 100 cells/microliter on highly active antiretroviral therapies, the numbers of patients who have been evaluated are insufficient to warrant a recommendation to discontinue prophylaxis.

Special Considerations

Children

6. Although no specific data are available regarding coccidioidomycosis in HIV-infected children, a reasonable option is to administer lifelong suppressive therapy after an acute episode of the disease (rating: AIII).

Pregnant Women

7. The potential teratogenicity of fluconazole (Pursley et al, 1996; Alec & Barley, 1997) and itraconazole (CDC, 2000) should be considered when assessing the therapeutic options for HIV-infected women who become pregnant while receiving chronic maintenance therapy for coccidioidomycosis. For such patients, therapy with amphotericin B may be preferred, especially during the first trimester. For women receiving highly active antiretroviral therapies with a sustained rise in CD4+ T lymphocyte counts above 100 cells/microliter, discontinuation of azole prophylaxis, especially during the first trimester, should be considered. Effective birth control measures should be recommended for all HIV-infected women on azole therapy for coccidioidomycosis (rating: AIII).

Cytomegalovirus Disease

Prevention of Exposure

1. HIV-infected persons who belong to risk groups with relatively low rates of seropositivity for cytomegalovirus (CMV) and who therefore cannot be presumed to be seropositive should be tested for antibody to cytomegalovirus

(rating: BIII). These groups include patients who have not had male homosexual contact or used injection drugs.

2. HIV-infected adolescents and adults should be advised that cytomegalovirus is shed in semen, cervical secretions, and saliva and that latex condoms must always be used during sexual contact to reduce the risk for exposure to cytomegalovirus and to other sexually transmitted pathogens (rating: AII).
3. HIV-infected adults and adolescents who are child-care providers or parents of children in child-care facilities should be informed that they are at increased risk for acquiring cytomegalovirus infection (rating: BI). Similarly, parents and other caretakers of HIV-infected children should be advised of the increased risk to children at these centers (rating: BIII). The risk for acquiring cytomegalovirus infection can be diminished by good hygienic practices such as hand washing (rating: AII).
4. HIV-exposed infants and HIV-infected children, adolescents, and adults who are seronegative for cytomegalovirus and require blood transfusion should be administered only cytomegalovirus antibody-negative or leukocyte-reduced cellular blood products in nonemergency situations (rating: BIII).

Prevention of Disease

5. Prophylaxis with oral ganciclovir may be considered for HIV-infected adults and adolescents who are cytomegalovirus seropositive and who have a CD4+ T-lymphocyte count of less than 50 cells/microliter (rating: CI) (Spector et al, 1996; Brosgart et al, 1998). Ganciclovir-induced neutropenia, anemia, conflicting reports of efficacy, lack of proven survival benefit, the risk for developing ganciclovir-resistant cytomegalovirus, and cost are among the issues that should be considered when deciding whether to institute prophylaxis in individual patients. Acyclovir is not effective in preventing cytomegalovirus disease, and valacyclovir is not recommended because of an unexplained trend toward increased deaths among persons with AIDS who were administered valacyclovir for cytomegalovirus prophylaxis (Feinberg et al, 1998). Therefore, neither acyclovir nor valacyclovir should be used for this purpose (rating: EI). The most important method for preventing severe cytomegalovirus disease is recognition of the early manifestations of the disease. Early recognition of cytomegalovirus retinitis is most likely when the patient has been educated on this topic. Patients should be made aware of the significance of increased floaters in the eye and should be advised to assess their visual acuity regularly by using simple techniques such as reading newsprint (rating: BIII). Regular funduscopic examinations performed by an ophthalmologist are recommended by some experts for patients with low (e.g., less than 50 cells/microliter) CD4+ T-lymphocyte counts (rating: CIII).

Prevention of Recurrence

6. Cytomegalovirus disease is not cured with courses of the currently available antiviral agents (e.g., ganciclovir, foscarnet, or cidofovir). Following induction therapy, secondary prophylaxis (chronic maintenance therapy) is recommended for life (rating: AI), unless there is immune reconstitution as a consequence of highly active antiretroviral therapies (see Recommendation No. 7, below). Regimens that are effective for chronic suppression include parenteral or oral ganciclovir, parenteral foscarnet, combined parenteral

ganciclovir and foscarnet, parenteral cidofovir, and (for retinitis only) ganciclovir administration via intraocular implant or repetitive intravitreous injections of fomivirsen (rating: AI) (Martin et al, 1999; Drew et al, 1995; Studies of Ocular Complications of AIDS Research Group in Collaboration with the AIDS Clinical Trials Groups, 1997; Palestine et al, 1991; Spector et al, 1993; Studies of Ocular Complications of AIDS in collaboration with the AIDS clinical Trials Group, 1996; Diaz-Llopis et al, 1994; Lewis et al, 1997; DeSmet, Meenken, & van den Horn, 1999). Oral valganciclovir has been approved by the U.S. Food and Drug Administration (FDA) for both acute induction therapy and for maintenance therapy although much of the data have not been published. Repetitive intravitreous injections of ganciclovir, foscarnet, and cidofovir have been reported to be effective for secondary prophylaxis of cytomegalovirus retinitis in uncontrolled case series (Kirsch et al, 1995; Young et al, 1998). The intraocular implant alone does not provide protection to the contralateral eye or to other organ systems. The choice of a chronic maintenance regimen for patients treated for cytomegalovirus disease should be made in consultation with an expert. For patients with retinitis, this decision should be made in consultation with an ophthalmologist and should take into consideration the anatomic location of the retinal lesion, vision in the contralateral eye, the immunologic and virologic status of the patient, and the patient's response to highly active antiretroviral therapies (rating: BIII).

Discontinuation of Secondary Prophylaxis (Chronic Maintenance Therapy)

7. Several case series have reported that maintenance therapy can be discontinued safely in adult and adolescent patients with cytomegalovirus retinitis whose CD4+ T-lymphocyte counts have shown a sustained (e.g., $\geq$6 months) increase to >100 to 150 cells/microliter in response to highly active antiretroviral therapies (Tural et al, 1998; Vrabec, Baldassano, & Whitcup, 1998; MacDonald et al, 1998; Whitcup et al, 1999; Jabs et al, 1998; Jouan et al, 2001). These patients have remained disease-free for greater than 30 to 95 weeks, whereas in the pre- highly active antiretroviral therapies era, retinitis typically reactivated within 6 to 8 weeks after stopping cytomegalovirus therapy. Plasma HIV ribonucleic acid levels were variable in these patients, suggesting that the CD4+ T-lymphocyte count is the primary determinant of immune recovery to cytomegalovirus. Discontinuation of prophylaxis should be considered in patients with a sustained, (e.g., $\geq$6 months) increase in CD4+ T-lymphocyte count to >100 to 150 cells/microliter in response to highly active antiretroviral therapies (rating: BII). Such decisions should be made in consultation with an ophthalmologist and should take into account such factors as magnitude and duration of CD4+ T-lymphocyte increase, anatomic location of the retinal lesion, vision in the contralateral eye, and the feasibility of regular ophthalmologic monitoring (rating: BII). All patients who have had anti-cytomegalovirus maintenance therapy discontinued should continue to undergo regular ophthalmologic monitoring for early detection of cytomegalovirus relapse (as well as for immune reconstitution uveitis) (rating: AIII). Cytomegalovirus viral load or other markers of cytomegalovirus infection, e.g., antigenemia, or viral deoxyribonucleic acid (DNA) tests are not well standardized; their role in predicting relapse remains to be defined (Spector et al, date not specified; Salmon-Cerm et al, 2000). Relapses have been reported rarely in patients

with CD4+ T lymphocyte count >100 to 150 cells/microliter (Torriani et al, 2000).

Restarting Secondary Prophylaxis

8. Relapse of cytomegalovirus retinitis occurs in patients whose anti-cytomegalovirus retinitis maintenance therapy has been discontinued and whose CD4+ T-lymphocyte count has decreased to <50 cells/microliter (Kirsch et al, 1995). Therefore, reinstitution of secondary prophylaxis should be reinstituted when the CD4+ T-lymphocyte count has decreased to <100 to 150 cells/microliter (rating: AIII). Relapse has been reported in patients whose CD4+ T lymphocyte counts are higher then 100 cells/microliter, but such reports are rare to date (Torriani et al, 2000).

Special Considerations

Children

9. Some experts recommend obtaining a cytomegalovirus urine culture on all HIV-infected (or exposed) infants at birth or at an early postnatal visit to identify those infants with congenital cytomegalovirus infection (rating: CIII). In addition, beginning at 1 year of age, cytomegalovirus antibody testing on an annual basis may be considered for cytomegalovirus-seronegative (and culture-negative) HIV-infected infants and children who are severely immunosuppressed (see Table 9 in the original guideline document) (rating: CIII). Annual testing will allow identification of children who have acquired cytomegalovirus infection and might benefit from screening for retinitis.
10. HIV-infected children who are cytomegalovirus-infected and severely immunosuppressed might benefit from a dilated retinal examination performed by an ophthalmologist every 4 to 6 months (rating: CIII). In addition, older children should be counseled to be aware of floaters in the eye, similar to the recommendation for adults (rating: BIII).
11. Oral ganciclovir results in reduced cytomegalovirus shedding in cytomegalovirus-infected children and may be considered for primary prophylaxis against cytomegalovirus disease in CMV-infected children who are severely immunosuppressed (e.g., CD4+ T-lymphocyte count less than 50 cells/microliter) (rating: CII).
12. Patients with a history of cytomegalovirus retinitis disease should be administered lifelong prophylaxis to prevent recurrence (rating: AII). For children with cytomegalovirus disease, no data are available to guide decisions concerning discontinuation of secondary prophylaxis (chronic maintenance therapy) when the CD4+ T-lymphocyte count has increased in response to highly active antiretroviral therapies.

Pregnant Women

13. Indications for prophylaxis are the same for pregnant women as for non-pregnant women. The choice of agents to be used in pregnancy should be individualized after consultation with experts.

Herpes Simplex Virus Disease

Prevention of Exposure

1. HIV-infected persons should use latex condoms during every act of sexual intercourse to reduce the risk for exposure to herpes simplex virus (HSV) and to other sexually transmitted pathogens (rating: AII). They should specifically avoid sexual contact when herpetic lesions (genital or orolabial) are evident (rating: AII).

Prevention of Disease

2. Prophylaxis of initial episodes of herpes simplex virus disease is not recommended (rating: DIII).

Prevention of Recurrence

3. Because acute episodes of herpes simplex virus infection can be treated successfully, chronic therapy with acyclovir is not required after lesions resolve. However, persons who have frequent or severe recurrences can be administered daily suppressive therapy with oral acyclovir or oral famciclovir (rating: AI) (Schacker et al., 1998; Schacker, Hu, Koelle, et al., 1998). Valacyclovir also is an option (rating: CIII). Intravenous foscarnet or cidofovir can be used to treat infection due to acyclovir-resistant isolates of herpes simplex virus, which are routinely resistant to ganciclovir as well (rating: AII).

Special Considerations

Children

4. The recommendations for preventing initial disease and recurrence among adults and adolescents apply to children as well.

Pregnant Women

5. Oral acyclovir prophylaxis during late pregnancy is a controversial strategy recommended by some experts to prevent neonatal herpes transmission. However, such prophylaxis is not routinely recommended. For patients who have frequent, severe recurrences of genital herpes simplex virus disease, acyclovir prophylaxis might be indicated (rating: BIII). No pattern of adverse pregnancy outcomes has been reported after acyclovir exposures (CDC, 1993).

Varicella-Zoster Virus Infection

Prevention of Exposure

1. HIV-infected children and adults who are susceptible to varicella-zoster virus (VZV) (i.e., those who have no history of chickenpox or shingles or are seronegative for varicella-zoster virus) should avoid exposure to persons with chickenpox or shingles (rating: AII). Household contacts (especially children) of susceptible HIV-infected persons should be vaccinated against varicella-

zoster virus if they have no history of chickenpox and are seronegative for HIV, so that they will not transmit varicella-zoster virus to their susceptible HIV-infected contacts (rating: BIII).

Prevention of Disease

2. Very little data regarding the safety and efficacy of varicella vaccine in HIV-infected adults are available, and no recommendation for its use can be made for this population. (See the section/subsection titled "Special Considerations/Children," below, for information about the use of varicella vaccine in children.)
3. For the prophylaxis of chickenpox, HIV-infected children and adults who are susceptible to varicella-zoster virus (i.e., those who have no history of chickenpox or shingles or who have no detectable antibody against varicella-zoster virus) should be administered varicella zoster immune globulin (VZIG) as soon as possible but within 96 hours after close contact with a patient who has chickenpox or shingles (rating: AIII). Data are lacking on the effectiveness of acyclovir for preventing chickenpox in susceptible HIV-infected children or adults.
4. No preventive measures are currently available for shingles.

Prevention of Recurrence

5. No drug has been proven to prevent the recurrence of shingles in HIV-infected persons.

Special Considerations

Children

6. HIV-infected children who are asymptomatic and not immunosuppressed (i.e., in immunologic category 1, see Table 9 in the original guideline document) should receive live attenuated varicella vaccine at 12 to 15 months of age or later (rating: BII). Varicella vaccine should not be administered to other HIV-infected children because of the potential for disseminated viral infection (rating: EIII).

Pregnant Women

7. Varicella zoster immune globulin is recommended for varicella-zoster virus - susceptible, HIV-infected pregnant women within 96 hours after exposure to varicella-zoster virus (rating: AIII). If oral acyclovir is used, varicella-zoster virus serology should be performed so that the drug can be discontinued if the patient is seropositive for varicella-zoster virus (rating: BIII).

<u>Human Herpesvirus 8 Infection (Kaposi's Sarcoma - Associated Herpes Virus)</u>

Prevention of Exposure

1. Persons co-infected with HIV and human herpesvirus 8 (HHV-8) are at risk for developing Kaposi's sarcoma (KS), and, there is evidence that progression to Kaposi's sarcoma may be accelerated in individuals who seroconvert to human herpesvirus 8 after being infected with HIV. Thus it is important to prevent acquisition of human herpesvirus 8 infections in those already infected with HIV (Jacobson et al, 2000; Renwick et al, 1998; Martin et al, 1998). The three major routes of human herpesvirus 8 transmission appear to be oral (the virus infects oral epithelial cells, and infection has been associated with deep kissing in one study), via semen (human herpesvirus 8 is less frequently detected in semen than in saliva), and through blood via needle sharing (Pauk et al, 2000; Cannon et al, 2001; Whitby et al, 1999). Patients should be counseled that deep kissing and sexual intercourse with individuals who have high risk of being infected with human herpesvirus 8, e.g., persons who have Kaposi's sarcoma or who are infected with HIV, may lead to acquisition of the agent that causes Kaposi's sarcoma (rating: CIII). Although the efficacy of condom use for preventing human herpesvirus 8 infection exposure has not been established, HIV-infected persons should use latex condoms during every act of sexual intercourse to reduce exposure to sexually transmitted pathogens (rating: AII). HIV-infected injection drug users should be counseled to not share drug injection equipment, even if both users are already HIV-infected, because of the chance of becoming infected with human herpesvirus 8 or other bloodborne pathogens (rating: BIII).

Prevention of Disease

2. Because clinical use of routine serologic testing to identify human herpesvirus 8 infection has not been established, no recommendation for serologic testing can be made at this time.
3. Lower rates of Kaposi's sarcoma have been observed among AIDS patients treated with ganciclovir or foscarnet for cytomegalovirus retinitis (Feinberg et al, 1998). Human herpesvirus 8 replication in vitro is inhibited by ganciclovir, foscarnet, and cidofovir. However, because the efficacy and clinical use of these drugs in preventing Kaposi's sarcoma have not been established, no recommendation can be made concerning the use of these or other drugs to prevent Kaposi's sarcoma in individuals coinfected with HIV and human herpesvirus 8.
4. Potent antiretroviral drug combinations that suppress HIV replication reduce the frequency of Kaposi's sarcoma in HIV-infected persons (Ledergerber et al, 1999) and should be considered for all persons who qualify for such therapy (rating: BII).

Prevention of Recurrence

5. Effective suppression of HIV replication with antiretroviral drugs in HIV-infected patients with Kaposi's sarcoma might prevent Kaposi's sarcoma progression or the development of new lesions and should be considered for all persons with Kaposi's sarcoma (rating: BII).

Special Considerations

Children

6. In parts of the world where human herpesvirus 8 is endemic, mother-to-child transmission of human herpesvirus-8 has been reported and (Bourboulia et al, 1998; He et al, 1998; Sitas, Newton, & Boshoff, 1999; Plancoulaine et al, 2000) horizontal transmission might occur among young children, possibly via saliva. However, no recommendations are currently available for preventing human herpesvirus 8 transmission from child to child.

Human Papillomavirus Infection

Prevention of Exposure

1. HIV-infected persons should use latex condoms during every act of sexual intercourse to reduce the risk for exposure to sexually transmitted pathogens (rating: AII), although little evidence exists to suggest that condoms reduce the risk for infection with human papillomavirus (HPV).

Prevention of Disease

Human Papillomavirus-Associated Genital Epithelial Cancers in HIV-infected Women

2. After a complete history of previous cervical disease has been obtained, HIV-infected women should have a pelvic examination and a Pap smear. In accordance with the recommendation of the former Agency for Health Care Policy and Research (now the Agency for Healthcare Quality and Research), the Pap smear should be obtained twice in the first year after diagnosis of HIV infection and, if the results are normal, annually thereafter (rating: AII).
3. If the results of the Pap smear are abnormal, care should be provided according to the Interim Guidelines for Management of Abnormal Cervical Cytology published by a National Cancer Institute Consensus Panel and briefly summarized in Recommendations 4 through 8, which follow (Kurman et al, 1994).
4. For patients whose Pap smears are interpreted as atypical squamous cells of undetermined significance (ASCUS), several management options are available; the choice depends in part on whether the interpretation of atypical squamous cells of undetermined significance is qualified by a statement indicating that a neoplastic process is suspected. Follow-up by Pap tests without colposcopy is acceptable, particularly when the diagnosis of atypical squamous cells of undetermined significance is not qualified further or the cytopathologist suspects a reactive process. In such situations, Pap tests should be repeated every 4 to 6 months for 2 years until three consecutive smears have been negative. If a second report of atypical squamous cells of undetermined significance occurs in the 2-year follow-up period, the patient should be considered for colposcopic evaluation (rating: BIII).
5. Women who have a diagnosis of unqualified atypical squamous cells of undetermined significance associated with severe inflammation should be evaluated for an infectious process. If specific infections are identified, reevaluation should be performed after appropriate treatment, preferably after 2 to 3 months (rating: BIII).
6. If the diagnosis of atypical squamous cells of undetermined significance is qualified by a statement indicating that a neoplastic process is suspected, the patient should be managed as if a low-grade squamous intraepithelial lesion

(LSIL) were present (see Recommendation 7, below) (rating: BIII). If a patient who has a diagnosis of atypical squamous cells of undetermined significance is at high risk (i.e., previous positive Pap tests or poor adherence to follow-up), the option of colposcopy should be considered (rating: BIII).

7. Several management options are available for patients who have low-grade squamous intraepithelial lesion. Follow up with Pap tests every 4 to 6 months is used by many clinicians and is currently used in countries outside the United States as an established method of management. Patients managed in this way must be carefully selected and considered reliable for follow-up. If repeat smears show persistent abnormalities, colposcopy and directed biopsy are indicated rating: BIII). Colposcopy and directed biopsy of any abnormal area on the ectocervix constitute another appropriate option (rating: BIII).
8. Women who have cytologic diagnosis of high-grade squamous intraepithelial lesions (HSILs) or squamous cell carcinoma should undergo colposcopy and directed biopsy (rating: AII).
9. No data are available to suggest that these guidelines to prevent cervical disease should be modified for women on highly active antiretroviral therapies.

Human Papillomavirus-Associated Anal Intraepithelial Neoplasia and Anal Cancer in HIV-infected Men Who Have Sex With Men and in Women

10. Evidence from several studies shows that human papillomavirus-positive men who have sex with men are at increased risk for anal high-grade squamous intraepithelial lesions and might be at increased risk for anal cancer. In view of this evidence, coupled with a recent cost-effectiveness analysis projecting that screening and treatment for anal high-grade squamous intraepithelial lesions provide clinical benefits comparable to other measures to prevent opportunistic infections in HIV-infected persons (He et al, 1998), anal cytology screening of HIV-infected men who have sex with men might become a useful preventive measure in the near future. However, further studies of screening and treatment programs for anal high-grade squamous intraepithelial lesions need to be carried out before recommendations for routine anal cytology screening can be made.

Prevention of Recurrence

11. The risks for recurrence of squamous intraepithelial lesions and cervical cancer after conventional therapy are increased among HIV-infected women. The prevention of illness associated with recurrence depends on careful follow-up of patients after treatment. Patients should be monitored with frequent cytologic screening and, when indicated, with colposcopic examination for recurrent lesions (rating: AI) (Kurman et al, 1994; Saves et al, 2000).
12. In one recent study of HIV-infected women treated for high-grade squamous intraepithelial lesions using standard therapy, low-dose intravaginal 5-fluorouracil (2 grams twice a week for 6 months) reduced the short-term risk for recurrence and possibly the grade of recurrence (Maiman et al, 1999). However, clinical experience with this therapy is too limited to provide a recommendation for routine use.

Special Considerations

Pregnant Women

13. Use of intravaginal 5-fluorouracil to prevent recurrent dysplasia is not recommended during pregnancy.

Hepatitis C Virus Infection

Prevention of Exposure

1. The chief route of hepatitis C virus (HCV) transmission in the United States is injection drug use. Because injection drug use is a complex behavior, clinicians should assess the individual's readiness to change this practice and encourage efforts to provide patient education and support directed at recovery.

   Patients who inject drugs should be advised (CDC, 1998; Sulkowski et al, 2000; Darby et al, 1997)

   - To stop using injection drugs (rating: AIII); and
   - To enter and complete a substance-abuse treatment program, including a relapse prevention program (rating: AIII).

   If they are continuing to inject drugs, patients should be advised (rating: BIII):

   - To never reuse or share syringes, needles, water, or drug preparation equipment; if, nonetheless, injection equipment that has been used by other persons is shared, to first clean the equipment with bleach and water as is recommended for prevention of HIV;
   - To use only sterile syringes obtained from a reliable source (e.g., pharmacies or syringe exchange programs);
   - To use sterile (e.g., boiled) water to prepare drugs; if not possible, to use clean water from a reliable source (e.g., fresh tap water);
   - To use a new or disinfected container ("cooker") and a new filter ("cotton") to prepare drugs;
   - To clean the injection site with a new alcohol swab before injection; and
   - To safely dispose of syringes after one use.
2. Persons considering tattooing or body piercing should be informed of potential risks of acquiring bloodborne infections, which could be transmitted if equipment is not sterile or if proper infection control procedures are not followed (e.g., washing hands, using latex gloves, and cleaning and disinfecting surfaces) (Darby et al, 1997) (rating: BIII).
3. To reduce risks for acquiring bloodborne infections, patients should be advised not to share dental appliances, razors, or other personal care articles (rating: BIII).
4. Although the efficiency of sexual transmission of hepatitis C virus remains controversial, safe-sexual practices should be encouraged, and barrier precautions (e.g., latex condoms) are recommended to reduce the risk for exposure to sexually transmitted pathogens (rating: AII).

5. All patients with HIV infection should be screened for hepatitis C virus infection (rating: BIII). Screening is recommended because some HIV-infected patients (e.g., injection drug users, and patients with hemophilia) are at increased risk for hepatitis C virus infection and hepatitis C virus related disease, and because knowledge of hepatitis C virus status is important for management of all HIV-infected patients (e.g., to interpret and manage elevated results from liver-related tests). Screening should be performed by using enzyme immunoassays (EIAs) licensed for detection of antibody to hepatitis C virus (anti-hepatitis C virus) in blood (rating: BIII). Positive anti-hepatitis C virus results should be verified with additional testing (i.e., recombinant immunoblot assay [RIBA(TM)] or reverse transcriptase polymerase chain reaction for hepatitis C virus ribonucleic acid). The presence of hepatitis C virus ribonucleic acid in blood might also be assessed in HIV-infected persons with undetectable antibody but other evidence of chronic liver disease (e.g., unexplained elevated liver-specific enzymes) or when acute hepatitis C virus infection is suspected (rating: CIII).
6. Persons coinfected with HIV and hepatitis C virus should be advised not to drink excessive amounts of alcohol (rating: AII). Avoiding alcohol altogether might be prudent because it is unclear whether even occasional moderate alcohol use (e.g., less than 12 ounces of beer or less than 10 grams of alcohol per week) increases the incidence of cirrhosis among hepatitis C virus-infected persons (rating: CIII).
7. Patients with chronic hepatitis C should be vaccinated against hepatitis A because (a) the risk for fulminant hepatitis associated with hepatitis A appears increased in hepatitis C virus-coinfected persons; (b) hepatitis A vaccine is safe for HIV-infected persons; and (c) although immunogenicity is reduced in patients with advanced HIV infection, more than two thirds of patients develop protective antibody responses (rating: BIII). Prevaccination screening for antibody to hepatitis A virus is cost-effective and therefore recommended when greater than 30% prevalence of hepatitis A virus antibody is expected in the population being screened (e.g., persons greater than 40 years of age) (Eyster et al., 1993) (rating: BIII). Patients should also be immunized for hepatitis B virus if they are susceptible (rating: BIII).
8. HIV-hepatitis C virus-coinfected patients may develop hepatitis C virus associated liver disease over a shorter time course than patients infected with hepatitis C virus alone (Darby et al, 1997; Thomas et al, 1996; Rodriguez-Rosado, 1998; Saves et al, 2000) and should be evaluated for chronic liver disease and for the possible need for treatment. Limited data suggest that hepatitis C virus treatment can be safely provided to patients coinfected with HIV and hepatitis C virus. Because the optimal means of treating coinfected patients has not been established and many HIV-infected patients have conditions that complicate therapy (e.g., depression or illicit drug use), this care should occur in a clinical trial or be coordinated by providers with experience treating both HIV and hepatitis C virus infections (rating: BIII).
9. In some studies, the incidence of antiretroviral-associated liver enzyme elevations has been increased in patients coinfected with HIV and hepatitis C virus (Thomas et al, 1996); such increases might not require treatment modifications. Thus, although liver enzymes should be carefully monitored, highly active antiretroviral therapies should not be routinely withheld from patients coinfected with HIV and hepatitis C virus (rating: DIII). However, coinfected patients initiating antiretroviral therapy might have an

inflammatory reaction that mimics an exacerbation of underlying liver disease. In this situation, careful monitoring of liver function is required.

Prevention of Recurrence

10. If the serum hepatitis C virus ribonucleic acid level becomes undetectable during hepatitis C virus therapy and remains undetectable for 6 months after hepatitis C virus therapy is stopped (sustained virologic response), greater than 90% of HIV-uninfected patients with hepatitis C will remain hepatitis C virus ribonucleic acid negative for greater than 5 years and have improved liver histology (Chemello et al, 1996). For HIV-hepatitis C virus-coinfected patients, the durability of treatment response and requirement for maintenance therapy are unknown.

Special Considerations

Children

11. Transmission of hepatitis C virus from mother to child appears to be more frequent for mothers co-infected with HIV and hepatitis C virus than for those infected with hepatitis C virus alone. Therefore, children born to women coinfected with HIV and hepatitis C virus should be tested for hepatitis C virus infection (CDC, 1998) (rating: BI). Because maternal hepatitis C virus antibody can persist for up to 18 months, and hepatitis C virus ribonucleic acid can be intermittently undetectable. Thus, testing should be performed at or after 2 years of age. If earlier diagnosis is needed, hepatitis C virus ribonucleic acid should be assessed in more than one infant blood specimen obtained after 1 month of age. The average rate of hepatitis C virus infection among infants born to coinfected women is approximately 15% (range, 5% to 36%) (Mast & Alter, 1997). Data are limited on the natural history and treatment of hepatitis C virus infection in children.

Recommendations to Help Patients Avoid Exposure to or Infection with Opportunistic Pathogens

Sexual Exposures

1. Patients should use a latex condom during every act of sexual intercourse to reduce the risk for acquiring cytomegalovirus, herpes simplex virus, and human papillomavirus, as well as other sexually transmitted pathogens (rating: AII). Condom use also will, theoretically, reduce the risk for acquiring human herpesvirus 8, as well as superinfection with an HIV strain that has become resistant to antiretroviral drugs (rating: BIII) and will prevent transmission of HIV and other sexually transmitted pathogens to others (rating: AII). Data regarding the use and efficacy of female condoms are incomplete, but these devices should be considered as a risk-reduction strategy (rating: BIII).
2. Patients should avoid sexual practices that might result in oral exposure to feces (e.g., oral-anal contact) to reduce the risk for intestinal infections (e.g., cryptosporidiosis, shigellosis, campylobacteriosis, amebiasis, giardiasis, and hepatitis A) (rating: BIII). Latex condom use alone may not reduce the risk of acquiring these fecal-orally transmitted pathogens, especially those which

have low infectious doses. Persons wishing to reduce their risk of exposure might consider using dental dams or similar barrier methods for oral-anal and oral-genital contact, changing condoms after anal intercourse, and wearing latex gloves during digital-anal contact. Frequently washing hands and genitals with warm soapy water during and after activities which may bring these body parts in contact with feces may further reduce risk of illness (rating: CIII).

3. Hepatitis B immunizations is recommended for all susceptible (anti-HBc-negative) HIV-infected patients (rating: BII).
4. Hepatitis A immunization is recommended for all susceptible men who have sex with men, as well as others with indications for hepatitis A virus vaccine (rating: BIII).

Injection Drug Use Exposures

1. Injection drug use is a complex behavior that puts HIV-infected persons at risk for hepatitis C virus infection, additional, possibly drug-resistant strains of HIV, and other blood-borne pathogens. Providers should assess the individual's readiness to change this practice and encourage efforts to provide education and support directed at recovery. Patients should be counseled to stop using injection drugs (rating: AIII) and to enter and complete substance-abuse treatment, including relapse prevention programs (rating: AIII).
2. If they are continuing to inject drugs, patients should be advised (rating: BIII):
    - To never reuse or share syringes, needles, water, or drug preparation equipment; if, nonetheless, injection equipment that has been used by other persons is shared, to first clean the equipment with bleach and water (U.S. Public Health Service. HIV prevention bulletin: medical advice for persons who inject illicit drugs. May 8, 1997. Rockville, Maryland: Centers for Disease Control and Prevention, 1997);
    - To use only sterile syringes obtained from a reliable source (e.g., pharmacies or syringe exchange programs);
    - To use sterile (e.g., boiled) water to prepare drugs; if not possible, to use clean water from a reliable source (e.g., fresh tap water); to use a new or disinfected container ("cooker") and a new filter ("cotton") to prepare drugs;
    - To clean the injection site with a new alcohol swab before injection;
    - To safely dispose of syringes after one use.
3. All susceptible injection drug users should be immunized against hepatitis B (rating: BII) and hepatitis A (rating: BIII).

Environmental and Occupational Exposures

1. Certain activities or types of employment might increase the risk for exposure to tuberculosis (rating: BIII). These include volunteer work or employment in healthcare facilities, correctional institutions, and shelters for the homeless, as well as other settings identified as high risk by local health authorities. Decisions about whether to continue with such activities should be made in conjunction with the healthcare provider and should be based on such factors as the patient's specific duties in the workplace, the prevalence of tuberculosis in the community, and the degree to which precautions designed

to prevent the transmission of tuberculosis are taken in the workplace (rating: BIII). These decisions will affect the frequency with which the patient should be screened for tuberculosis.

2. Child-care providers and parents of children in child care are at increased risk for acquiring cytomegalovirus infection, cryptosporidiosis, and other infections (e.g., hepatitis A and giardiasis) from children. The risk for acquiring infection can be diminished by good hygienic practices, such as hand washing after fecal contact (e.g., during diaper changing) and after contact with urine or saliva (rating: AII). All children in child-care facilities also are at increased risk for acquiring these same infections; parents and other caretakers of HIV-infected children should be advised of this risk (rating: BIII).
3. Occupations involving contact with animals (e.g., veterinary work and employment in pet stores, farms, or slaughterhouses) might pose a risk for cryptosporidiosis, toxoplasmosis, salmonellosis, campylobacteriosis, or Bartonella infection. However, the available data are insufficient to justify a recommendation against work in such settings.
4. Contact with young farm animals, especially animals with diarrhea, should be avoided to reduce the risk for cryptosporidiosis (rating: BII).
5. Hand washing after gardening or other contact with soil might reduce the risk for cryptosporidiosis and toxoplasmosis (rating: BIII).
6. In areas endemic for histoplasmosis, patients should avoid activities known to be associated with increased risk (e.g., creating dust when working with surface soil; cleaning chicken coops that are heavily contaminated with compost droppings; disturbing soil beneath bird-roosting sites; cleaning, remodeling or demolishing old buildings; and cave exploring) (rating: CIII).
7. In areas endemic for coccidioidomycosis, when possible, patients should avoid activities associated with increased risk, including those involving extensive exposure to disturbed native soil (e.g., at building excavation sites or during dust storms) (rating: CIII).

Pet-Related Exposures

Health-care providers should advise HIV-infected persons of the potential risk posed by pet ownership. However, they should be sensitive to the possible psychological benefits of pet ownership and should not routinely advise HIV-infected persons to part with their pets (rating: DIII). Specifically, providers should advise HIV-infected patients of the following precautions.

General

1. Veterinary care should be sought when a pet develops diarrheal illness. If possible, HIV-infected persons should avoid contact with animals that have diarrhea (rating: BIII). A fecal sample should be obtained from animals with diarrhea and examined for Cryptosporidium, Salmonella, and Campylobacter.
2. When obtaining a new pet, HIV-infected patients should avoid animals aged younger than 6 months (or younger than 1 year for cats; see section titled "Cats," below), especially those with diarrhea (rating: BIII). Because the hygienic and sanitary conditions in pet-breeding facilities, pet stores, and animal shelters are highly variable, the patient should be cautious when obtaining a pet from these sources. Stray animals should be avoided. Animals aged younger than 6 months, especially those with diarrhea, should be

examined by a veterinarian for Cryptosporidium, Salmonella, and Campylobacter (rating: BIII).
3. Patients should wash their hands after handling pets (especially before eating) and avoid contact with pets' feces to reduce the risk for cryptosporidiosis, salmonellosis, and campylobacteriosis (rating: BIII). Hand washing for HIV-infected children should be supervised.

Cats

4. Patients should be aware that cat ownership increases their risk for toxoplasmosis and Bartonella infection, as well as enteric infections (rating: CIII). Those who elect to obtain a cat should adopt or purchase an animal that is aged older than 1 year and in good health to reduce the risk for cryptosporidiosis, Bartonella infection, salmonellosis, and campylobacteriosis (rating: BII).
5. Litter boxes should be cleaned daily, preferably by an HIV-negative, nonpregnant person; if the HIV-infected patient performs this task, he or she should wash hands thoroughly afterward to reduce the risk for toxoplasmosis (rating: BIII).
6. To reduce the risk for toxoplasmosis, HIV-infected patients should keep cats indoors, not allow them to hunt, and not feed them raw or undercooked meat (rating: BIII).
7. Although declawing is not generally advised, patients should avoid activities that might result in cat scratches or bites to reduce the risk for Bartonella infection (rating: BII). Patients should also wash sites of cat scratches or bites promptly (rating: CIII) and should not allow cats to lick the patients' open cuts or wounds (rating: BIII).
8. Care of cats should include flea control to reduce the risk for Bartonella infection (rating: CIII).
9. Testing cats for toxoplasmosis (rating: EII) or Bartonellainfection (rating: DII) is not recommended.

Birds

10. Screening healthy birds for Cryptococcus neoformans, Mycobacterium avium, or Histoplasma capsulatum is not recommended (rating: DIII).

Other

11. Contact with reptiles (e.g., snakes, lizards, iguanas, and turtles) as well as chicks and ducklings should be avoided to reduce the risk for salmonellosis (rating: BIII).
12. Gloves should be used during the cleaning of aquariums to reduce the risk for infection with Mycobacterium marinum (rating: BIII).
13. Contact with exotic pets (e.g., nonhuman primates) should be avoided (rating: CIII).

Food-and Water-Related Exposures

1. Raw or undercooked eggs (including foods that might contain raw eggs [e.g., some preparations of hollandaise sauce, Caesar and certain other salad dressings, and some mayonnaises, uncooked cookie and cake batter, egg

nog]); raw or undercooked poultry, meat, seafood (especially raw shellfish); and unpasteurized dairy products; unpasteurized fruit juice; and raw seed sprouts (e.g., alfalfa sprouts, mung bean sprouts). Poultry and meat are safest when adequate cooking is confirmed with a thermometer (internal temperature of 180 degrees F for poultry and 165 degrees F for red meats). If a thermometer is not used, the risk of illness is decreased by consuming poultry and meat that have no trace of pink. Color change of the meat (e.g., absence of pink) does not always correlate with internal temperature. Produce should be washed thoroughly before being eaten (rating: BIII).

2. Cross-contamination of foods should be avoided. Uncooked meats should not be allowed to come in contact with other foods; hands, cutting boards, counters, and knives and other utensils should be washed thoroughly after contact with uncooked foods (rating: BIII).
3. Although the incidence of listeriosis is low, it is a serious disease that occurs unusually frequently among HIV-infected persons who are severely immunosuppressed. An immunosuppressed, HIV-infected person who wishes to reduce the risk of acquiring listeriosis as much as possible may choose to do the following: (1) avoid soft cheeses (e.g., feta, Brie, Camembert, blue-veined and Mexican-style cheese such as queso fresco). Hard cheeses, processed cheeses, cream cheese (including slices and spreads), cottage cheese, or yogurt need not be avoided; (2) cook leftover foods or ready-to-eat foods (e.g., hot dogs) until steaming hot before eating; (3) avoid foods from delicatessen counters (e.g., prepared salads, meats, cheeses) or heat/reheat these foods until steaming before eating; (4) avoid refrigerated pates and other meat spreads, or heat/reheat these foods until steaming if eaten. Canned or shelf-stable pate and meat spreads need not be avoided; (5) avoid raw or unpasteurized milk (including goat's milk) or milk-products, or foods which contain unpasteurized milk or milk-products. (rating: CIII).
4. Patients should not drink water directly from lakes or rivers because of the risk for cryptosporidiosis and giardiasis (rating: AIII). Waterborne infection might also result from swallowing water during recreational activities. Patients should avoid swimming in water that is likely to be contaminated with human or animal waste and should avoid swallowing water during swimming (rating: BII).
5. During outbreaks or in other situations in which a community "boil water advisory" is issued, boiling water for 1 minute will eliminate the risk for acquiring cryptosporidiosis (rating: AI). Using submicron, personal-use water filters (home/office types) and/or drinking bottled water might also reduce the risk (see the section titled "Cryptosporidiosis" under the "Disease-Specific Recommendations," above, for information on personal-use filters and bottled water) (rating: CIII). Current data are inadequate to support a recommendation that all HIV-infected persons boil or otherwise avoid drinking tap water in nonoutbreak settings. However, persons who wish to take independent action to reduce their risk for waterborne cryptosporidiosis may choose to take precautions similar to those recommended during outbreaks. Such decisions are best made in conjunction with a health-care provider. Persons who opt for a personal-use filter or bottled water should be aware of the complexities involved in selecting the appropriate products, the lack of enforceable standards for destruction or removal of oocysts, the cost of the products, and the difficulty of using these products consistently. Patients taking precautions to avoid acquiring cryptosporidiosis from drinking water should be advised that ice made from contaminated tap water also can be a source of infection (rating: BII). Such persons should be aware that fountain

beverages served in restaurants, bars, theaters, and other public places might also pose a risk, because these beverages, as well as the ice they might contain, are made from tap water. Nationally distributed brands of bottled or canned carbonated soft drinks are safe to drink. Commercially packaged noncarbonated soft drinks and fruit juices that do not require refrigeration until after they are opened (i.e., those that can be stored unrefrigerated on grocery shelves) also are safe. Nationally distributed brands of frozen fruit juice concentrate are safe if they are reconstituted by the user with water from a safe source. Fruit juices that must be kept refrigerated from the time they are processed to the time of consumption might be either fresh (unpasteurized) or heat-treated (pasteurized); only juices labeled as pasteurized should be considered free of risk from Cryptosporidium. Other pasteurized beverages and beers are also considered safe to drink (rating: BII). No data are available concerning survival of Cryptosporidium oocysts in wine.

Travel-Related Exposures

1. Travel, particularly to developing countries, might result in significant risks for the exposure of HIV-infected persons to opportunistic pathogens, especially for patients who are severely immunosuppressed. Consultation with health-care providers and/or with experts in travel medicine will help patients plan itineraries (rating: BIII).
2. During travel to developing countries, HIV-infected persons are at even higher risk for foodborne and waterborne infections than they are in the United States. Foods and beverages -- in particular, raw fruits and vegetables, raw or undercooked seafood or meat, tap water, ice made with tap water, unpasteurized milk and dairy products, and items purchased from street vendors -- might be contaminated (rating: AII). Items that are generally safe include steaming-hot foods, fruits that are peeled by the traveler, bottled (especially carbonated) beverages, hot coffee or tea, beer, wine, and water brought to a rolling boil for 1 minute (rating: AII). Treating water with iodine or chlorine might not be as effective as boiling but can be used, perhaps in conjunction with filtration, when boiling is not practical (rating: BIII).
3. Waterborne infections might result from swallowing water during recreational activities. To reduce the risk for cryptosporidiosis and giardiasis, patients should avoid swallowing water during swimming and should not swim in water that might be contaminated (e.g., with sewage or animal waste) (rating: BII).
4. Antimicrobial prophylaxis for traveler's diarrhea is not recommended routinely for HIV-infected persons traveling to developing countries (rating: DIII). Such preventive therapy can have adverse effects and can promote the emergence of drug-resistant organisms. Nonetheless, several studies (none involving an HIV-infected population) have shown that prophylaxis can reduce the risk for diarrhea among travelers (CDC. Health information for international travel, 1999-2000. Atlanta, Georgia: United States Department of Health and Human Services, 1999:202). Under selected circumstances (e.g., those in which the risk for infection is very high and the period of travel brief), the provider and patient may weigh the potential risks and benefits and decide that antibiotic prophylaxis is warranted (rating: CIII). For those persons to whom prophylaxis is offered, fluoroquinolones (e.g., ciprofloxacin

[500 mg daily]) can be considered (rating: BIII), although fluoroquinolones should not be given to children or pregnant women. Trimethoprim-sulfamethoxazole (trimethoprim-sulfamethoxazole) (one double-strength tablet daily) also has been shown to be effective, but resistance to this drug is now common in tropical areas. Persons already taking trimethoprim-sulfamethoxazole for prophylaxis against Pneumocystis carinii pneumonia might gain some protection against traveler's diarrhea. For HIV-infected persons who are not already taking trimethoprim-sulfamethoxazole, healthcare providers should be cautious in prescribing this agent for prophylaxis of diarrhea because of the high rates of adverse reactions and the possible need for the agent for other purposes (e.g., Pneumocystis carinii pneumonia prophylaxis) in the future.

5. All HIV-infected travelers to developing countries should carry a sufficient supply of an antimicrobial agent to be taken empirically should diarrhea develop (rating: BIII). One appropriate regimen is 500 mg of ciprofloxacin twice a day for 3 to 7 days. Alternative antibiotics (e.g., trimethoprim-sulfamethoxazole) should be considered as empirical therapy for use by children and pregnant women (rating: CIII). Travelers should consult a physician if their diarrhea is severe and does not respond to empirical therapy, if their stools contain blood, if fever is accompanied by shaking chills, or if dehydration develops. Antiperistaltic agents (e.g., diphenoxylate and loperamide) are used for the treatment of diarrhea; however, they should not be used by patients with high fever or with blood in the stool, and their use should be discontinued if symptoms persist beyond 48 hours (rating: AII). Antiperistaltic agents are not recommended for children (rating: DIII).
6. Travelers should be advised about other preventive measures appropriate for anticipated exposures (e.g., chemoprophylaxis for malaria, protection against arthropod vectors, treatment with immune globulin, and vaccination) (rating: AII). They should avoid direct contact of the skin with soil or sand (e.g., by wearing shoes and protective clothing and using towels on beaches) in areas where fecal contamination of soil is likely (rating: BIII).
7. In general, live-virus vaccines should be avoided (rating: EII). One exception is measles vaccine, which is recommended for nonimmune persons. However, measles vaccine is not recommended for persons who are severely immunosuppressed (rating: DIII); immune globulin should be considered for measles-susceptible, severely immunosuppressed persons who are anticipating travel to measles-endemic countries (rating: BIII). Another exception is varicella vaccine, which may be administered to asymptomatic nonimmunosuppressed children (rating: BII). Inactivated (killed) poliovirus vaccine should be used instead of oral (live) poliovirus vaccine, which is contraindicated for HIV-infected persons. Persons at risk for exposure to typhoid fever should be administered an inactivated parenteral typhoid vaccine instead of the live attenuated oral preparation. Yellow fever vaccine is a live-virus vaccine with uncertain safety and efficacy in HIV-infected persons. Travelers with asymptomatic HIV infection who cannot avoid potential exposure to yellow fever should be offered the choice of vaccination. If travel to a zone with yellow fever is necessary and vaccination is not administered, patients should be advised of the risk, instructed in methods for avoiding the bites of vector mosquitoes, and provided with a vaccination waiver letter.
8. In general, killed and recombinant vaccines (e.g., diphtheria-tetanus, rabies, hepatitis A, hepatitis B, Japanese encephalitis vaccines) should be used for HIV-infected persons just as they would be used for non-HIV-infected persons anticipating travel (rating: BIII). Preparation for travel should include a

review and updating of routine vaccinations, including diphtheria-tetanus for adults and all routine immunizations for children. The currently available cholera vaccine is not recommended for persons following a usual tourist itinerary, even if travel includes countries reporting cases of cholera (rating: DII).

9. Travelers should be informed about other area-specific risks and instructed in ways to reduce those risks (rating: BIII). Geographically focal infections that pose a high risk to HIV-infected persons include visceral leishmaniasis (a protozoan infection transmitted by the sandfly) and several fungal infections (e.g., Penicillium marneffei infection, coccidioidomycosis, and histoplasmosis). Many tropical and developing areas have high rates of tuberculosis.

Note: Refer to the original guideline document for specific information regarding the following:

- Dosages for prophylaxis to prevent first episode of opportunistic disease in HIV-infected adults and adolescents (Table 1).
- Dosages for prophylaxis to prevent recurrence of opportunistic disease in HIV-infected adults and adolescents (Table 2).
- Dosages of drugs for prevention of opportunistic infections for persons with renal insufficiency (Table 7).
- Immunologic categories for HIV-infected children (Table 9).
- Immunization schedule for HIV-infected children (Table 10).
- Dosages for prophylaxis to prevent first episode of opportunistic disease in HIV-infected infants and children (Table 11).
- Dosages for prophylaxis to prevent recurrence of opportunistic disease in HIV-infected infants and children (Table 12).
- Criteria for discontinuing and restarting opportunistic infection prophylaxis for adult patients with HIV infection (Table 13).

<u>System used to rate the strength of recommendations and quality of supporting evidence</u>

Rating: A
Strength of the recommendation: Both strong evidence for efficacy and substantial clinical benefit support recommendation for use.
Should always be offered.

Rating: B
Strength of the recommendation: Moderate evidence for efficacy -- or strong evidence for efficacy but only limited clinical benefit -- supports recommendation for use.
Should generally be offered.

Rating: C
Strength of the recommendation: Evidence for efficacy is insufficient to support a recommendation for or against use. Or evidence for efficacy might not outweigh adverse consequences (e.g., drug toxicity, drug interactions) or cost of the chemoprophylaxis or alternative approaches. Optional.

Rating: D
Strength of the recommendation: Moderate evidence for lack of efficacy or for

adverse outcome supports a recommendation against use. Should generally not be offered.

Rating: E
Strength of the recommendation: Good evidence for lack of efficacy or for adverse outcome supports a recommendation against use. Should never be offered.

Rating system used to determine quality of evidence supporting recommendation:

Category: I
Definition: Evidence from at least one properly randomized, controlled trial.

Category: II
Definition: Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than one center), or from multiple time-series. Or dramatic results from uncontrolled experiments.

Category: III
Definition: Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

REFERENCES SUPPORTING THE RECOMMENDATIONS

References open in a new window

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see â œMajor Recommendationsâ).

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Decreased incidence of opportunistic infection in patients with HIV
- Decreased morbidity and mortality
- Increased quality and duration of life

POTENTIAL HARMS

Adverse effects of opportunistic infection medications, including:

- Bone marrow suppression (cidofovir, dapsone, ganciclovir, pyrimethamine, rifabutin, sulfadiazine, trimethoprim-sulfamethoxazole, trimetrexate)
- Diarrhea (atovaquone, clindamycin)
- Hepatotoxicity (clarithromycin, fluconazole, isoniazid, itraconazole, ketoconazole, pyrazinamide, rifabutin, rifampin)
- Nephrotoxicity (amphotericin B, cidofovir, foscarnet, pentamidine)
- Ocular effects (cidofovir, ethambutol, rifabutin)
- Pancreatitis (pentamidine, trimethoprim-sulfamethoxazole)
- Peripheral neuropathy (isoniazid)
- Neurotoxicity [Acyclovir (high-dose), quinolones]
- Skin rash (atovaquone, dapsone, pyrimethamine, sulfadiazine, trimethoprim-sulfamethoxazole, ribavirin)

Other potential harms may include:

- Drug interactions
- Development of drug resistance

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Staying Healthy

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

2001 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus. Rockville (MD): U.S. Department of Health and Human Services, Public Health Service; 2001 Nov 28. 64 p. [145 references]

Centers for Disease Control and Prevention. Guidelines for preventing opportunistic infections among HIV-infected persons -- 2002. Recommendations

of the U.S. Public Health Service and the Infectious Diseases Society of America. MMWR Recomm Rep 2002 Jun 14;51(RR-8):1-52. [145 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1999 Aug (updated 2001 Nov 28)

GUIDELINE DEVELOPER(S)

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Infectious Diseases Society of America - Medical Specialty Society
Public Health Service (U.S.) - Federal Government Agency [U.S.]

SOURCE(S) OF FUNDING

United States Government

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USPHS/IDSA Prevention of Opportunistic Infections Working Group

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline. This guideline updates a previously released version: 1999 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus. MMWR Morb Mortal Wkly Rep 1999 Aug 20;48(RR-10).

Status information regarding this guideline is available from the AIDSinfo Web site, telephone (800) 448-0440, fax (301) 519-6616; TTY (888) 480-3739.

GUIDELINE AVAILABILITY

Electronic copies: Available from the AIDSinfo Web site.

Print copies: Available from the Centers for Disease Control and Prevention, National Prevention Information Network (NPIN), P.O. Box 6003, Rockville, MD 20850. Telephone: (800) 458-5231, TTY (800)-243-7012 International number (301)-562-1098. Web site: http://www.cdcnpin.org. Requests for print copies can also be submitted via the AIDSinfo Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- 2001 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus tool for Palm OS* or Pocket PC. The download is available from the AIDSinfo Web site.
- Guidelines for Environmental Infection Control in Health-Care Facilities. Recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee (HICPAC) (2003, Jun 6) avialable from the Centers for Disease Control and Prevention (CDC) Web site. This guideline provides supplemental information regarding patient interaction with pets and animals in the home.

PATIENT RESOURCES

Pamphlets for patients are available from the AIDSinfo Web site and also can be accessed via the Centers for Disease Control and Prevention (CDC) Division of HIV/AIDS Prevention Web site. In addition, the Appendix of the original guideline document presents recommendations to help patients avoid exposure to opportunistic infections. This Appendix is available (as part of the full-text guideline) from the AIDSinfo Web site.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC STATUS

This summary was completed by ECRI on January 24, 2001. The original information was verified by the guideline developer as of June 1, 2001.

Updated guidelines were most recently issued on November 28, 2001. This summary was updated most recently on December 17, 2001 in response to the updated guideline issued on November 28, 2001.

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